FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

Meeting Date:	15 April 2015
NDA:	204958
Sponsor:	The Medicines Company
Drug:	KENGREAL (cangrelor) for Injection
Proposed Indication for Use:	KENGREAL is an intravenous $P2Y_{12}$ platelet inhibitor indicated for reduction of thrombotic cardiovascular events in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI - PCI refers to the opening of narrowed blood vessels supplying the heart muscle by a balloon inserted through an artery puncture with or without a stent) who have not received an oral P2Y12 inhibitor prior to the PCI procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable (P2Y12 is a protein involved in blood clotting. Inhibiting this protein is a key mechanism of action of cangrelor).
Title of Study:	**PHOENIX** - A randomized, double-blind, parallel group, superiority study comparing cangrelor to clopidogrel in subjects who require PCI. The primary objective was to demonstrate that cangrelor reduces the risk of a composite of all-cause mortality, myocardial infarction, ischemia driven revascularization, and stent thrombosis compared to clopidogrel.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought cangrelor to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

This document is based on the applicant's information as submitted up to 17 March 2015.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

FDA White Oak Campus, Building 31, the Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
April 15, 2015

DRAFT POINTS TO CONSIDER

The April 15, 2015 meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) is the second advisory committee at which this NDA for cangrelor will be discussed. The Medicines Company submitted the NDA on April 20, 2013 but the FDA declined to approve it, detailing its reason for doing so in a Complete Response letter. The briefing documents for this meeting include the Office of Drug Evaluation 1 (ODE 1) decisional memo detailing the reasons for declining to approve the NDA and the clinical, statistical, and clinical pharmacology reviews of the applicant's responses to the Complete Response letter. The FDA and applicant briefing documents and presentations as well as the transcript of the discussion of the first CRDAC meeting are available at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm285415.htm

1. Background

Cangrelor, an analogue of adenosine triphosphate (ATP), is a parenteral, short-acting inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation. It directly and competitively inhibits ADP binding to the platelet P2Y12 receptor, one of the pathways that activate the platelet glycoprotein 2b/3a complex. The Medicines Company submitted an NDA seeking approval to market cangrelor for two indications:

1. Reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) and
2. To maintain P2Y12 inhibition in acute coronary syndromes (ACS) patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 inhibitor therapy is interrupted because of surgery (termed the 'Bridging' indication).

The applicant conducted three trials that were intended to provide substantial evidence of efficacy and safety to support approval for the PCI indication: CHAMPION PCI, CHAMPION PLATFORM, and CHAMPION PHOENIX. All three were large, randomized, double-blind superiority trials in which patients who had undergone coronary angiography were randomized immediately before percutaneous coronary intervention (PCI) to cangrelor administered as 30 µg/kg IV bolus followed by a 4 µg/kg/min infusion for at least 2 hours or until the conclusion of the index procedure (whichever was longer), followed by a 600 mg dose of clopidogrel, or to clopidogrel alone. The first two trials, PCI and PLATFORM, were conducted concurrently and were stopped at the same time prior to completion for futility. Post-hoc analyses of these two trials generated two hypotheses: 1) ascertainment of postprocedure MIs was masked by biomarker elevation related to a preprocedural MI obscuring cangrelor's efficacy and 2) cangrelor appeared to be effective in reducing the incidence of stent thrombosis (ST). The third trial, PHOENIX, was designed based on these two hypotheses. There are other potentially relevant differences between the first two trials and the third, which are summarized in the table below.

FOOD AND DRUG ADMINISTRATION

Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

April 15, 2015

DRAFT POINTS TO CONSIDER

Table 1: Differences amongst the CHAMPION Trials

		PHOENIX	PLATFORM	PCI
Dates of conduct		Sept 2010 – Nov 2012	Oct 2006 – July 2009	March 2006 – June 2009
Number of subjects (% of planned enrollment)		11145 (100%)	5364 (84%)	8846 (99%)
Primary endpoint		Death, MI, ischemia-driven revascularization (IDR), or stent thrombosis (including IPST) at 48 hrs	Death, MI, or IDR at 48 hrs	Death, MI, or IDR at 48 hrs
Outcome of primary analysis		OR: 0.79 (95% CI: 0.67, 0.93) p-value = 0.005	OR: 0.87 (95% CI: 0.71, 1.07) Nominal p-value = 0.18	OR: 1.05 (95% CI: 0.88 to 1.24) Nominal p-value = 0.59
Patients taking clopidogrel prior to enrollment		Not eligible to enroll	Not eligible to enroll	Eligible to enroll - 34% taking clopidogrel at baseline
Administration of study clopidogrel		300 or 600 mg either immediately before or after PCI	600 mg after PCI	600 mg immediately before PCI
Protocol restriction on use of glycoprotein 2b/3a inhibitors use		Bailout only	Initially at investigator discretion; use discouraged after May 8 2007	Initially at investigator discretion; use discouraged after May 8 2007
Actual glycoprotein 2b/3a use		Cangrelor: 2.3% Clopidogrel: 3.5%	8% (16% prior to May 8 2007)	22% (33% prior to May 8 2007)
Population enrolled	Stable angina	58%	5%	15%
	Non-ST elevation ACS	26%	95%	64%
	ST-elevation MI	16%	Not eligible to enroll	11%
Definition of MI used for primary endpoint		**Normal baseline CKMB**: CKMB ≥ 3x ULN **Abnormal baseline CKMB**: CKMB re- elevation + ischemic symptoms, angiographic evidence, or ECG changes **STEMI**: Not assessed	• Q-MI or • Postprocedure CKMB ≥ 3x ULN and CKMB > 50% above baseline if CKMB elevated prior to PCI	• Q-MI or • Postprocedure CKMB ≥ 3x ULN and CKMB > 50% above baseline if CKMB elevated prior to PCI

DRAFT POINTS TO CONSIDER

CHAMPION PHOENIX was statistically successful at a p-value of 0.005 and no novel safety issues were identified. The Division generally accepts a single trial with an active comparator that demonstrates superiority at p-value < 0.05 as adequate support for efficacy because that result provides strong evidence that the test drug is superior to placebo. The Division also believes that the failure of a previous trial or trials does not impugn the success of a subsequent trial or trials if the subsequent trial or trials were designed to address a hypothesis or hypotheses generated by the failed trials.

The application was discussed by the Cardiovascular and Renal Advisory Committee on February 12, 2014. The Committee voted 7-2 against approval for the PCI indication. The committee members who voted "No" indicated concern about the design of PHOENIX, about the two negative trials (PLATFORM and PCI), and also felt that the increased risk of bleeding was not outweighed by the small clinical benefit. In particular, the committee did not believe that reduction in the risk of intra-procedural stent thrombosis (IPST) was clinically important and expressed uncertainty about the clinical import of periprocedural MIs detectable only by rises in serum biomarkers. The committee voted 9-0 against approval for the Bridging indication. The committee unanimously concluded that the measure of platelet inhibition in this setting is an unproven surrogate and expressed concern that without a clinical trial in patients that assesses clinical outcome, the risks and benefits could not be known.

The Office of Drug Evaluation 1 declined to approve the NDA expressing concern about the following clinical/statistical issues related to the PCI indication:

1. Doubts about the clinical import of two subcomponents of the primary endpoint in PHOENIX: IPST and periprocedural myocardial MIs identified solely by increases in serum biomarkers of myocardial necrosis.

   IPST represents an angiographic finding identified during PCI and in the absence of consequent MI, does not result in permanent morbidity. The Division has never considered a similar claim previously and the Cardiac and Renal Drug Advisory Committee was skeptical about its meaningfulness. The Division noted the applicant's argument that observational studies suggest that patients who have IPST have worse outcomes, but believes such studies cannot distinguish whether IPST is itself a cause of such outcomes or merely identifies patients at higher risk for worse outcomes.

   The clinical importance of periprocedural MIs identified solely by increases in serum biomarkers of myocardial necrosis is unclear and continues to be debated. Although increases in postprocedural cardiac muscle biomarkers are associated with increased risk for subsequent cardiovascular events, it is again unclear whether they increase the risk of subsequent events or are simply a marker for subsequent events. Postprocedure measurement of serum biomarkers after uncomplicated PCI is not recommended in guidelines and apparently is not routine and so it appears that interventional cardiologists are not persuaded that postprocedural measurement of serum biomarkers in the absence of symptoms and/or ECG changes provides clearly useful prognostic information. The Division consulted the literature and identified a consensus document endorsed by the Society for Cardiovascular Angiography and Interventions (SCAI) (JACC 2013; 62:1563–70) that concluded that in patients without biomarker elevation prior to PCI the "preponderance of the best scientific evidence support(s) post-PCI elevation of CK-MB to ≥ 10x ULN as being clinically relevant."

To resolve the concern about IPST and periprocedural MIs that do not meet the criteria in the SCAI consensus document (SCAI MIs), the Division suggested to the applicant that they conduct a series of sensitivity analyses in which the primary endpoint is modified by removing those two subcomponents.

2. Difficulty in identifying a patient group in whom cangrelor is an appropriate therapeutic choice. The anti-platelet regimen used as the comparator in PHOENIX had several weaknesses relative to other regimens that are currently available: less inhibition of platelet aggregation, more interindividual variability in antiplatelet effect, and slower onset of action. Using stronger antiplatelet drugs might eliminate the utility of cangrelor.

   The protocol excluded patients who had been administered an oral P2Y12 inhibitor within seven days and enrollment did not occur until after angiography (except for STEMI patients who could be randomized prior to angiography). Hence clopidogrel was not administered until the start of PCI (and could be and was administered even later). Because clopidogrel takes a few hours to have maximal anti-platelet effect, delaying administration until PCI results in little or no anti-platelet effect during the procedure. It should be noted, however, that the 2011 ACCF/AHA/ SCAI Guideline for Percutaneous Coronary Intervention, while recommending that "a loading dose of an oral P2Y12 receptor inhibitor should be given to patients undergoing PCI with stenting," is noncommittal about precisely when the loading dose should be given. Moreover, more potent, more reliable, and faster acting oral P2Y12 inhibitors than clopidogrel are available as alternatives to cangrelor, which may limit the need for and utility of cangrelor.

   The protocol also restricted use of glycoprotein 2b/3a inhibitors (GPIs) to treatment for thrombotic complications of PCI; i.e. patients who in the opinion of the investigator required a GPI were excluded from enrolling. Compared to PCI and PLATFORM, substantially fewer subjects were administered a GPI in PHOENIX (see table 1). The current guidelines from American cardiology societies do not make clear recommendations about how to use these drugs as adjuncts to PCI because comparative studies directly testing them have not been performed (it should be noted that the current labels for these drugs provide no useful guidance). However, the guidelines seem to recommend selective use of GPIs in situations in which their more potent inhibition of platelet aggregation provides a benefit that justifies the increased risk of bleeding.

   To resolve these concerns, the Division suggested that the applicant provide background on current American practice on the use of adjunctive anti-platelet drugs during PCI to demonstrate the continued relevance of PHOENIX.

3. Uncertainty about whether the data from PHOENIX are sufficient to establish the utility of cangrelor for the treatment of patients with stable angina undergoing PCI. Patients with stable angina can be preloaded with a platelet P2Y12 receptor inhibitor before their angiography and if CABG is needed, it can be delayed for a week or so until the anti-platelet effects have diminished. Giving a P2Y12 receptor inhibitor prior to PCI may be preferable because it avoids the approximately two-hour post-PCI decrease in platelet inhibition that occurs after administration of cangrelor followed by clopidogrel.

To resolve this concern, the Division suggested that the applicant provide background information to understand current American practice regarding administration of oral P2Y12 inhibitors to stable angina patients referred for coronary angiography in anticipation of undergoing PCI.

4. Discrepancies in classification of subjects in PHOENIX as having stable angina, non-ST elevation ACS, or ST-elevation MI at the time of enrollment between that reported by the investigators in the IVRS at the time of randomization and that reported by applicant based on a post-hoc analysis. For about 20% of the subjects the classification reported by the investigators differed from that of the applicant. In the absence of evidence to the contrary, the Division believed practitioners deciding whether to use cangrelor would have about the same information as did PHOENIX investigators had when the decision was made to enroll the patient. If true, then the classification based on the investigators' assessments, while not necessarily more accurate, was more useful.

   To resolve the concern about how subjects should be classified for purposes of analysis, the Division asked the applicant to explain how and why they derived patient classification post hoc and why those classifications were more useful than the investigators' classifications.

The applicant is not seeking authorization to market cangrelor for the Bridging indication at this time and so the Division is not seeking further advice regarding this indication from the Cardiovascular and Renal Drugs Advisory Committee.

2. Discussion Topics

1. FDA requested that the applicant perform sensitivity analyses in which IPST and MIs not meeting the SCAI criteria for a clinically relevant MI are removed from the primary endpoint. The results of the prespecified primary analysis and the requested sensitivity analyses are shown below:

Table 2: Sensitivity Analyses of the Primary Endpoint at 48 Hours

Events	**Cangrelor** n (%)	**Clopidogrel** n (%)	**OR (95% CI)**	**Nominal p- value**
Death/MI/IDR/ST[1] (primary endpoint)	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)	.005
Death/MI/IDR/ARC-ST (primary endpoint excluding IPST)	230 (4.2)	286 (5.2)	0.80 (0.67, 0.95)	.012
Death/SCAI MI/IDR/ARC-ST (primary endpoint excluding IPST and MIs not meeting SCAI criteria)	79 (1.4)	114 (2.1)	0.69 (0.51, 0.92)	.011

[1] Includes IPST and stent thromboses meeting the Academic Research Consortium criteria (ARC-ST)

Do these sensitivity analyses provide adequate support for the notion that administration of cangrelor is beneficial? Has adequate evidence of efficacy been established?

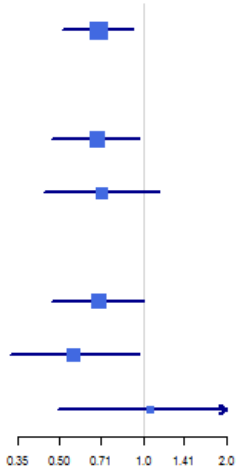
2. Were the subjects randomized to the comparator in PHOENIX treated in a manner consistent with current American standards of care? Does the comparator used render PHOENIX unable to demonstrate meaningful efficacy?

3. The applicant indicates that *ad hoc* PCI, in which patients with stable angina undergo angiography and PCI in the same session without being pretreated with an oral P2Y12 inhibitor, is a common practice in the USA. What are the advantages and disadvantages of this approach?

4. Subgroup analyses of the primary endpoint by subject presentation at the time of enrollment defined in two different ways are shown below. In one, patients are classified as having 1) stable angina, 2) non-ST elevation acute coronary syndrome (NSTE-ACS), and 3) ST-elevation myocardial infarction (STEMI), as is usually done in practice. In the other, they are classified as they were in the PHOENIX protocol for purposes of stratifying subjects as lower and higher risk for randomization. Subjects with either 1) STEMI or 2) NSTE-ACS with abnormal troponin at baseline or ongoing symptoms or ischemic ECG changes at baseline were classified as abnormal and constituted a higher risk subgroup.

Figure 1: Subgroup Analysis of Death/SCAI MI/IDR/ARC-ST at 48 Hours

	Cangrelor	Clopidogrel	OR (95% CI)
Overall	79/5470	114/5469	0.69 (0.51, 0.92)
Subject Stratum			
Normal	50/3549	73/3524	0.68 (0.47, 0.97)
Abnormal	29/1921	41/1945	0.71 (0.44, 1.15)
Clinical Presentation			
Stable Angina	45/3185	65/3171	0.69 (0.47, 1.01)
NSTE-ACS	21/1464	36/1428	0.56 (0.33, 0.97)
STEMI	13/821	13/870	1.06 (0.49, 2.30)



Please comment on whether you think there are significant differences in outcomes among these subgroups.

5. The FDA analyses of benefit and risk of administering cangrelor are shown below:

Table 3: PHOENIX Events and Number Needed to Treat

Events	Cangrelor (# subjects)	Clopidogrel (# subjects)	Number Needed to Treat
Death	18	18	-
SCAI MI, IDR, ARC-ST	61	96	156
SCAI MI	48	80	171
IDR	13	16	1822
ARC-ST	0	0	-

Note: if a subject had more than one event at 48 hours, then worst outcome counted (death >MI >IDR >ST)

Table 4: PHOENIX Events and Number Needed to Harm

Events	Cangrelor (# subjects)	Clopidogrel (# subjects)	Number Needed to Harm
GUSTO severe or moderate bleed	32	20	461
GUSTO severe	11	6	1106
GUSTO moderate	21	14	790
TIMI major or minor bleed	45	17	198
TIMI major	12	6	922
TIMI minor	33	11	251

Do the benefits of administering cangrelor for preventing periprocedural thrombotic events outweigh the risks?

6. Should cangrelor be approved as an adjunct to PCI for reducing the risk of periprocedural thrombotic events such as MI, stent thrombosis, and ischemia driven revascularization?

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA/BLA # **Supplement #**	204958
Applicant Name	The Medicines Company
Date of Submission	01 May 2013
PDUFA Goal Date	30 April 2014
Proprietary Name / **Established (USAN) Name**	KANGREAL/ cangrelor
Dosage Forms / Strength	Single-use 10 ml vial containing 50 mg cangrelor as a lyophilized powder for reconstitution
Proposed Indication(s)	I. Reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). II. To maintain $P2Y_{12}$ inhibition in acute coronary syndromes (ACS) patients or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery.
Action:	Complete Response for both indications

Material Reviewed/Consulted **OND Action Package, including:**	**Names of discipline reviewers**
Medical Officer Review Medical Team Leader Review	Fred Senatore, Nhi Beasley
Statistical Review	Jialu Zhang
Pharmacology Toxicology Review	Belay Tesfamariam
CMC Review/OBP Review	David J. Claffey
Microbiology Review	Steven P. Donald
Clinical Pharmacology Review	Sreedharan Sabarinath
OSI	Sharon Gershon
CDTL Review	Thomas Marciniak
OSE/DMEPA	Janine Stewart
OSE/DRISK	Somya Dunn
Deputy Division Director	Stephen Grant

OND=Office of New Drugs
OPDP=Office of Prescription Drug Products
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

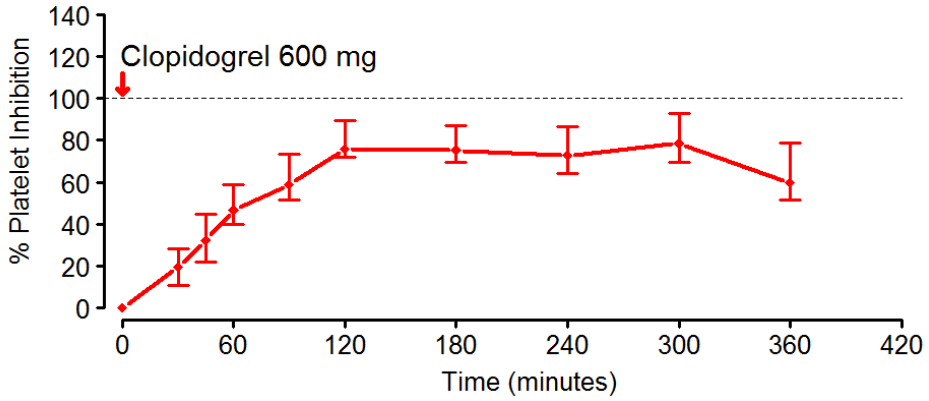
I. Introduction

Cangrelor is a parenterally administered inhibitor of adenosine-diphosphate (ADP)-induced platelet aggregation, inhibiting binding of ADP to the platelet P2Y12 receptor, the same receptor inhibited by clopidogrel's active metabolite and by prasugrel's active metabolites and reversibly inhibited by ticagelor. Cangrelor has a short half-life and its inhibition is rapidly reversible after infusion is stopped. Both of its proposed uses are intended to ameliorate problems associated with the PK/PD problems of clopidogrel when it is used 1) to treat patients undergoing percutaneous coronary intervention (PCI) or 2) to provide maintenance treatment in patients with a history of acute coronary syndromes or who have coronary stents in place, and who are going to surgery and need to stop drug.

1. PCI

In the first case, supported by the CHAMPION-PHOENIX study, it is well-recognized that platelet inhibition by clopidogrel takes about 2 hours to maximize, even with a 600 mg dose (twice the labeling-recommended dose) as shown in Dr. Grant's Figure 1, taken from Dr. Sabarinath's review. This is not an issue in a maintenance setting, but it can be in an acute setting. Thus, the striking early advantage of prasugrel over clopidogrel in the acute coronary syndrome (ACS) setting (TRITON Study) has been attributed in part to its rapid (no delay) effect, with a lesser difference seen later, attributed to prasugrel's overall greater platelet inhibition. Cangrelor is, in this case, being used to "cover" the 1-2 hour delay in attaining the full platelet-inhibiting effect of clopidogrel. This is, on its face, a pharmacologically and clinically reasonable approach, although one whose benefit cannot be expected to be large, as it would reduce, principally, events occurring in the first 1-2 hours of anti-platelet therapy. Indeed, as described below, this is where its effect appeared to occur.

Figure 1: Platelet inhibition over time of a 600 mg dose of clopidogrel



2. "Bridging" in maintenance clopidogrel therapy

Although there can be debate about how essential it is, labeling recommends that clopidogrel be discontinued 5 days before surgery to limit the risk of bleeding. Given that the loss of clopidogrel's effect would be potentially important at perhaps 1-2 days before surgery, and that few events would be likely to occur in that short time, the benefits of "bridging" the lost anti-platelet effect of clopidogrel with Cangrelor would be very modest at best and extremely difficult to detect in a trial. Nonetheless, basing a claim on clear evidence of an effect on platelet function during the 2-3 days before surgery, followed by drug withdrawal just before

the surgery, is not on its face unreasonable, although the Cardio-Renal Advisory Committee was plainly not convinced. It will be critical to see whether evidence of clinically meaningful anti-platelet activity (depending on the ultimate analysis of CHAMPION-PHOENIX) in a different setting can support this use, although it is recognized that the doses used in CHAMPION-PHOENIX were about 5 times larger. It is noted also that the use of cangrelor as a bridge led to increased bleeding.

II. Effectiveness in PCI

A variety of issues have arisen in the analysis and interpretation of the CHAMPION-PHOENIX results, principally relating to

1. The appropriateness of the study design, including timing of the control agent (clopidogrel) in relation to percutaneous coronary intervention (PCI), the dose of clopidogrel chosen (300 mg or 600 mg), and the ability to use 2b/3a inhibitors.

2. The meaningfulness of the observed effect on the 48 hour primary endpoint: death, new heart attack (MI), ischemia-driven revascularization (IDR), or stent thrombosis (ST). The primary endpoint assessed the comparative rates of occurrence of any of these events as the first event but secondary endpoint analyses included each event separately. An important concern was the clinical meaningfulness of some components of the primary endpoint, namely non-symptomatic (biomarker-based) myocardial infarctions and "intra-procedural stent thrombosis" (IPSTs), which together represent a substantial fraction of the primary endpoint events. It should be noted that we have accepted biomarker-based MIs as pertinent in assessment of prasugrel and ticagrelor.

   The study included 3 different populations: a) patients with stable angina (SA), b) patients with non-ST elevation acute coronary syndrome (NSTE-ACS), and c) patients with ST-elevation MI (STEMI). As will be considered further below, the need to delay clopidogrel until the start of PCI in the SA setting is open to question.

3. The importance of 2 other CHAMPION trials, CHAMPION-PLATFORM and CHAMPION-PCI, in different populations that failed to show a benefit of added Cangrelor (although CHAMPION-PLATFORM, in patients primarily with non-ST elevation ACS (NSTACS), leaned favorably).

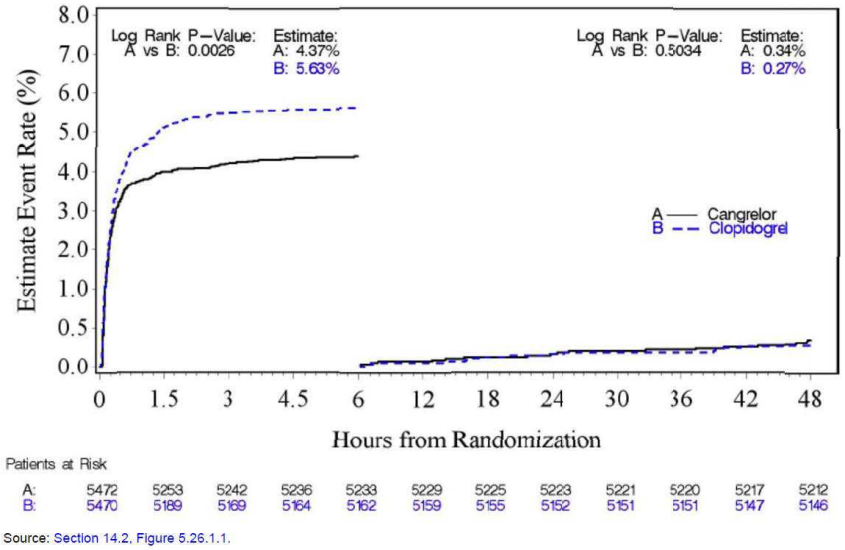
   A. Study Design of CHAMPION-PHOENIX
   An issue discussed in detail was whether initiation of clopidogrel was inappropriately delayed, giving cangrelor "more room" to show an advantage. It has been suggested that, particularly in the case of stable angina, clopidogrel could be started earlier, before angiography, and CABG delayed if angiography revealed a need for the surgical procedure If CABG were not indicated, PCI could proceed with the effect of clopidogrel fully manifested.

   Clopidogrel initiation was not markedly delayed but it was not given longer enough before PCI to be fully effective (which was, of course, why cangrelor was being used). Clopidogrel appears to have been started promptly, either before or shortly after PCI began, in most cases, as shown in Dr. Senatore's review pages 93-94. The sponsor contends (March 17, 2014, letter, p 19), and this is also shown in the forest plot on p 106 of Dr. Senatore's review, that hazard ratios for clopidogrel given before or after the start of PCI were essentially identical.

There is no doubt that the anti-platelet effect of clopidrogrel is somewhat greater, and occurs somewhat faster, with 600 mg of clopidogrel than with 300 mg, although clinical trials have generally not shown differences in effect. In CHAMPION-PHOENIX the dose of clopidogrel (600 or 300 mg) did not seem to make a difference in results (April 2, 2014 submission, p 18), with cangrelor somewhat better (HR 0.77) vs. 600 mg than 300 (HR 0.84), with about 75% of patients getting the 600 mg dose.

After 2 hours or completion of PCT, cangrelor was stopped and patients were given 600 mg of clopidogrel. It is stated in both the stats review and Dr. Senatore's review that the "loading dose" of clopidogrel was thus unbalanced, with 300 or 600 in the clopidogrel control group vs 600 in the Cangrelor group when Cangrelor was tapered and clopidogrel started. That, however, is not a loading dose, and is not part of the treatments being compared, and it followed the occurrence of most of the events of interest, as shown in the figure on p 60 of Dr. Senatore's review. The analysis of ST events above was similar.

Figure 9. Landmark analysis of first occurrence of death/MI/IDR/ST in 48 hours (mITT population)



Source: Section 14.2, Figure 5.26.1.1.

It is of interest, as stressed by Dr. Grant, that stopping cangrelor at 2 hours, then starting clopidogrel, leaves a relatively unprotected period from about 2-4 hours. This occurs because you cannot start clopidogrel until the cangrelor is gone from the blood. Although this could be troublesome, as it leaves the patient without anti-platelet coverage for 1-2 hours, most events had already occurred by 2 hours.

B. Importance of Endpoints and Effect

The primary endpoint in CHAMPION-PHOENIX was death, MI, ischemia-driven revascularization (IDR), and stent thrombosis (ST). There is no doubt as to the importance of death and IDR, nor of certain kinds of MI and ST, but the details bear discussion.

MI's with clear pain, q-wave effects, ST elevation, etc. are acknowledged to be bad events. But many MIs associated with procedures do not have such consequences. The PHOENIX trial used the "Universal definition of MI (UDMI), wherein an MI can be diagnosed if there were no prior enzyme elevations and CK-MB goes to 3xULN. If there was evidence of ischemia at baseline, a new MI needed either clear resolution of the baseline ischemia or new findings (ECG changes, symptoms, etc).

Although there was some skepticism as to the importance of these "biomarker MIs," FDA has accepted them in the TRITON study of prasugrel and the applicant argues that they have adverse consequences, a matter the applicant will need to address fully.

The ST endpoint included intra-procedural stent thrombosis (IPST), i.e., new or worsened thrombosis during the procedure, as well as post procedural ST, which all accept as a significant event. The applicant argues that these IPST events predict a bad outcome but that leaves open the question of whether it was the event or the patient's susceptibility to such an event that was critical. This too will need to be addressed further.

Of interest is a table in Dr. Grant's review, based on Dr. Zhang's analysis,

Table 2: Outcomes up to 48 hours in CHAMPION-PHOENIX (mITT)

Outcome	Cangrelor N = 5472		Clopidogrel N = 5470		
	events	%	events	%	OR (95% CI)
Death/MI/IDR/ST (primary endpoint)	257	4.7	322	5.9	0.78 (0.66, 0.93)
Death/MI/IDR/ARC* ST (i.e., primary endpoint excluding IPST)	230	4.2	286	5.2	0.79 (0.66, 0.95)
Death/MI (CKMB > 10x ULN for subjects with baseline normal CKMB)/IDR/ARC ST (i.e., primary endpoint excluding MIs with < 10 X ULN CKMB)	86	1.6	116	2.1	0.74 (0.56, 0.98)

* Academic Research Consortium
** Death, MI (checkbox on MI CRF), unplanned revascularization or stent thrombosis (checkboxes on revasc CRF)

that removes the questioned endpoints, notably any MI with < 10x ULN increase in CKMB and any intra-procedural ST (IPST), leaving only bona fide ST's. The HRs remain unaltered, although confidence intervals widen. There is thus nominal significance for the endpoint that includes death, real ST, IDR, and a reasonably strongly supported MI. This important result will need to be assessed and confirmed by the applicant.

It is also notable, as shown in Dr. Senatore's forest plot (p 106), that effects on the primary endpoint are quite similar for all 3 subgroups of the population. These are also presented in the sponsor's March 17, 2014 submission.

Group	Cangrelor	Clopidogrel	OR (95% CI)
All Patients	257/5470 (4.7%)	322/5469 (5.9%)	0.79 (0.67, 0.93)
Stable Angina	181/3120 (5.8%)	222/3018 (7.4%)	0.78 (0.63, 0.95)
NSTE/ ACS	49/1389 (3.8%)	62/1421 (4.4%)	0.80 (0.55,1.17)
STEMI	27/961 (2.8%)	38/1030 (3.7%)	0.75 (0.46, 1.25)

I note, however, that there is some uncertainty as to classification of patients, as discussed fully in Dr. Zhang's statistical Review Addendum. The table above is based on the "derived" patient type, a determination that modified the site-reported patient type based on additional information not available to the site investigator. Somewhat surprisingly, the results were quite different.

	Cangrelor	Clopidogrel	OR (95% CI)
Stable Angina	182/3185 (5.7%)	217/3171 (6.8%)	0.83 (0.67, 1.01)
NSTE/ACS	53/1464 (3.0%)	82/1428 (5.7%)	0.62 (0.43, 0.88)
STEMI	22/821 (2.7%)	23/870 (2.0%)	1.01 (0.56, 1.83)

This will need further discussion and explanation by the applicant, pertinent more to labeling than to evidence of overall effectiveness.

III. Previous Trials

The critical features of the CHAMPION-PCI and CHAMPION-PLATFORM trials are set out in Dr. Grant's Deputy Director review. Both trials entered patients with much more aggressive CAD, 95% NSTEMI/ACS in PLATFORM and 75% NSTEMI/ACS or STEMI in CHAMPION-PCI. Both used a clopidogrel dose of 600 mg, just prior to PCI in CHAMPION-PCI and after PCI in CHAMPION-PLATFORM and used endpoints of death, MI, IRR at 48 hours (but not ST). In PCI about 1/3 of patients were already receiving clopidogrel and 2b/3a inhibitors were used in about 25%. The PCI study did not suggest any effect (HR 1.05) but PLATFORM "leaned" (HR 0.87). It seems likely that prior use of clopidogrel and use of 2b/3a inhibitors worked against cangrelor in the PCI study. The applicant also believes many pre-existing MIs (surely more likely in these more acutely ill patients) were mistakenly counted as "new MIs," undermining any cangrelor effect. To avoid this in PHOENIX, patients with elevated CKMB were generally not counted as new MIs.

Like Dr. Grant, if PHOENIX were persuasive at a reasonably strong significance level, I believe the two negative studies would not weigh heavily against a conclusion of effectiveness.

IV. Bridging Study

I am less negative than the Advisory Committee on the possibility of a pharmacologically based conclusion that bridging is effective, given the clear evidence of an ability to replace the anti-platelet effect lost when clopidogrel is stopped prior to surgery. It is clear, however, that the added 2 or so days of coverage will not prevent very many stent thromboses and there clearly will be some excess of bleeding. Whether this use represents a reasonable benefit-risk tradeoff clearly

needs further consideration and perhaps more use data, at least to define risk. It seems unlikely that a study large enough to show an actual reduction in ST in this short period is feasible.

V. Data Issues

Apart from the analysis of results in the entry subsets (see IIB above) there needs to be further evaluation of the late "unlocking" of the database (see Dr. Grant's review) and of results omitting the questionable endpoints of IPST and small CKMB MIs. The potential importance of those endpoints can also be further addressed by the applicant.

VI. Conclusion

I do not believe cangrelor can be approved at this time for use in reducing thrombotic events in patients undergoing PCI or as a bridge to maintain platelet inhibition in patients with a history of ACS or patients with stents when clopidogrel therapy must be interrupted because of pending surgery. There is evidence that tends to support the first of these claims but there remain important questions of what populations would benefit from the use of cangrelor (stable angina, NSTE/ACS, STEMI) and in what patients clopidogrel should be delayed until PCI is begun (although it does appear this is relatively common practice. It will be critical to assess the effect of cangrelor on clearly pertinent endpoints (death, post procedure ST, IDR and longer CKMB MIs) even if the drug's effect on IPST and smaller MIs is given some weight. The applicant will be asked to address these issues further.

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/s/

ROBERT TEMPLE
04/30/2014

CLINICAL REVIEW OF RESUBMISSION

Application Type	NDA, Class 2 resubmission
Application Number(s)	204958
Initial Submission Date	30 April 2013
Advisory Committee Meeting Dates	12 February 2014, 15 April 2015
Complete Response Letter Date	30 April 2014
Resubmission Date	23 December 2014, submission 063
PDUFA Goal Date	23 June 2015
Division / Office	Division of Cardiovascular and Renal Products /Office of Drug Evaluation 1
Reviewer Names	Fred Senatore, MD, PhD, FACC (efficacy) B. Nhi Beasley, Pharm.D. (safety)
Review Completion Date	19 March 2015
Established Name	Cangrelor
(Proposed) Trade Name	Kengreal™
Therapeutic Class	$P2Y_{12}$ platelet inhibitor
Applicant	The Medicines Company
Formulation(s)	Intravenous
Dosing Regimen	30 ug/kg IV bolus followed by 4 ug/kg/min infusion for a minimum of 2 hours or the duration of PCI
Indication(s)	Reduction of thrombotic cardiovascular events in patients undergoing percutaneous coronary intervention (PCI)
Intended Population(s)	Patients with coronary artery disease undergoing PCI who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable.

Template Version: March 6, 2009

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List of Abbreviations

ARC	Academic Research Consortium
ARC-ST	ARC-defined ST
CDTL	Cross-Discipline Team Leader (FDA role)
CEC	Clinical Endpoint Committee (i.e. adjudication committee)
CHAMPION	Cangrelor versus standard therapy to achieve optimal management of platelet inhibition
CI	Confidence Interval
CK-MB	Creatinine kinase myocardial b fraction
COR	Class of Recommendation
CR	Complete Response
CSR	Case Study Report
IPA	Inhibition of Platelet Aggregation
IPST	Intraprocedural Stent Thrombosis
IR	Information Request
ITT	Intention to treat
LOE	Level of Evidence
MI	Myocardial Infarction
mITT	Modified Intention to treat
NSTE-ACS	Non-ST segment elevation acute coronary syndrome
NSTEMI	Non-ST segment elevation myocardial infarction
OR	Odds Ratio
OSI	Office of Scientific Investigation
PEP	Primary endpoint
QW	Q-wave
QWMI	Q-wave Myocardial Infarction
SA	SA
SAP	Statistical Analysis Plan
SCAI	Society for Cardiac Angiography and Interventions
SOP	Standard Operating Procedure
ST	Stent Thrombosis
STEMI	ST segment elevation myocardial infarction
UA	Unstable Angina
ULN	Upper limit of normal

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We recommend that cangrelor be approved as an adjunct to percutaneous coronary intervention (PCI) for the reduction in risk of periprocedural ischemic complications including myocardial infarction and stent thrombosis in patients in whom treatment with an oral $P2Y_{12}$ platelet inhibitor prior to PCI is not feasible and when glycoprotein IIb/IIIa receptor antagonists are not anticipated to be used.

1.2 Benefit Risk Assessment

The primary efficacy endpoint (PEP) included death, myocardial infarction (MI), ischemia driven revascularization (IDR), and stent thrombosis (ST) at 48 hours after randomization. Secondary endpoints included components of the composite; they were ordered and tested sequentially. The applicant won on the PEP (p=0.005), the MI component (p=0.02), and the ST component (p=0.01). ***Table 1*** shows the PEP, its components and various subtypes for the modified Intention-to-Treat population (mITT).

Table 1. CHAMPION PHOENIX endpoints, mITT population[1]

	Cangrelor N=5472 (%)	Clopidogrel N=5470 (%)	OR (95% CI)
Death, MI, IDR, ST (Primary endpoint)	257 (4.7)	322 (5.9)	0.78 (0.66, 0.93)[a]
Death	18 (0.3)	18 (0.3)	--
Myocardial infarction (MI)[2]	207 (3.8)	255 (4.7)	0.80 (0.67, 0.97)
Type 1	1 (0.0)	1 (0.0)	--
Type 3	3 (0.1)	0 (0.0)	--
Type 4a (associated with PCI)	194 (3.5)	239 (4.4)	0.80 (0.66, 0.98)
Type 4b (associated with ST)	9 (0.2)	15 (0.3)	0.60 (0.26, 1.37)
MI by SCAI	53 (1.0)	81 (1.5)	0.65 (0.46, 0.92)[b]
Q-wave	11 (0.2)	18 (0.3)	0.61 (0.29, 1.29)
Ischemia Driven Revascularization	28 (0.2)	38 (0.7)	0.74 (0.45, 1.20)
Stent Thrombosis	46 (0.8)	74 (1.4)	0.62 (0.43, 0.90)
Intraprocedural ST	35 (0.6)	54 (1.0)	0.65 (0.42, 0.99)
Academic Research Consortium ST[3]	12 (0.2)	22 (0.4)	0.54 (0.27, 1.10)

Adapted from CHAMPION PHOENIX CSR Table 5.1.1.1
a=adjusted prespecified primary endpoint analysis
b=adapted from Applicant's Complete Response document, Table 12.
-- Not calculated or reviewer chose not to show
SCAI=Society for Cardiovascular Angiography and Interventions, OR=odds ratio.
MI types and SCAI MI[3] defined in *Section 7.2*.

Each component will be discussed separately in order of clinical import. Mortality in CHAMPION PHOENIX was the same in both arms at 48 hours (18 vs. 18). At 30 days, there were 60 deaths in the cangrelor arm (1.1%) and 55 deaths in the clopidogrel arm (1.0%) in the mITT population.[4] Because death was balanced between arms, it did not impact our benefit risk assessment.

Myocardial infarction was defined by the Universal Definition of MI (UDMI).[5] Most of the MIs were associated with PCI (Type 4a). Periprocedural myocardial necrosis was defined as elevations of cardiac biomarkers 3x above the 99th percentile upper limit of normal (ULN) in patients with normal baseline cardiac biomarkers. Thus, angiographic evidence, ECG changes, or ischemic symptoms were not required for the diagnosis of a periprocedural MI. The Society for Cardiovascular Angiography and Interventions

1 The mITT population was defined as subjects that received at least one dose of study drug and had the index PCI. The number of subjects that did not complete follow-up in the mITT population were 2 and 1, cangrelor and clopidogrel, respectively. The ITT results for the PEP included 3 additional events in each arm. The incidence and OR were similar among the ITT and the mITT population.

2 Total MI= Type 1+Type 3+Type 4a+Type 4b. Type 1, 3, 4b, and all Q-wave MIs except one Q-wave MI are included in the subjects with SCAI MI.

3 ARC-ST data were all Definite ST. There was no Probable or Possible ST.

4 Reviewer's analysis: rb\nnt, Dataset: endpoint

5 Thygesen et al. Circulation 2007; 116: 2634-2653.

(SCAI) endorsed an Expert Consensus Document[6] that states that in patients with normal baseline cardiac biomarkers prior to PCI the "preponderance of the best scientific evidence supports post-PCI elevation of CK-MB ≥ 10x ULN as being clinically relevant". This document therefore questions the clinical meaningfulness of periprocedural MIs in CHAMPION PHOENIX that were diagnosed solely by 3x ULN< CK-MB < 10x ULN. Consequently, in our benefit risk analysis we included MIs as defined by SCAI.

Ischemia driven revascularization represents a failed PCI. In CHAMPION PHOENIX, IDR was defined as rest pain (presumed to be ischemic) resulting in urgent (not planned/staged) repeat PCI or urgent coronary artery bypass graft surgery. In the absence of pain, other ischemic symptoms (e.g., ventricular arrhythmia) sufficed if they occurred after completion of the index PCI and guide wire removal.[7] Avoidance of revascularization is a clinical benefit.

Like IDR, stent thrombosis represents a failed PCI. Stent thrombosis is a rare event but can lead to MI or death, so avoidance of ST is also a clinical benefit. Several drugs (including glycoprotein IIb/IIIa inhibitors (GPI) and other $P2Y_{12}$ inhibitors) reduce the occurrence of ST. The applicant's definition of ST included ARC ST and intraprocedural ST (IPST). ARC ST occurs after the patient has left the catheterization lab and is an established definition developed by the Academic Research Consortium (ARC).[8] IPST represented an angiographic finding identified during PCI, but its prognostic significance has never been demonstrated.

Table 2 shows the benefit of cangrelor relative to clopidogrel in CHAMPION PHOENIX. There were a total of 79 subjects on cangrelor and 114 subjects on clopidogrel that died, or had an MI defined by SCAI, or had IDR, or had ARC-ST within 48 hours of randomization. We believe that the clinical meaningfulness of these endpoints is unlikely to be disputed. In the benefit analysis shown in ***Table 2***, subjects are counted by worst event and are counted only once. If a subject had more than one event in 48 hours, the worst event was counted as death>SCAI MI > IDR > ST (e.g., a subject with an SCAI MI and an ARC-ST is counted only in SCAI MI.). The number needed to treat was not calculated for deaths and ARC-ST since it was neutral.

6 Moussa ID et al. Journal of American College of Cardiology 2013; 62: 1563-70.
7 Unlike the ARC definition of a target lesion revascularization that requires symptoms and target lesion severity of >50% diameter stenosis, there was no minimum diameter stenosis required. Percent diameter stenosis was recorded in ~ 75% of subjects who were revascularized with PCI; there was no difference between treatment arms (mean stenosis~89%).
8 Cutlip DE et al., Academic Research Consortium. Circulation 2007;115:2344-2351

Table 2. PHOENIX Subjects with efficacy event and number needed to treat

	Cangrelor N=5470 (%)	Clopidogrel N=5469 (%)	Number Needed to Treat
Death	18 (0.33)	18 (0.33)	---
SCAI MI, IDR, ARC-ST	61 (1.12)	96 (1.76)	156
SCAI MI	48 (0.88)	80 (1.46)	171
IDR	13 (0.24)	16 (0.29)	1822
ARC-ST	0 (0.00)	0 (0.00)	---

Reviewer's analysis: rb\nnt, mITT population. Dataset: ep_scai. Subjects counted only once and by worst event. For subjects with more than one event in 48 hours, the worst event was counted (death>SCAI MI > IDR > ARC-ST).

Table 3 shows the number need to harm, with the primary safety concern being major bleeding. Subjects are counted only once within each bleed classification.

Table 3. PHOENIX Subjects with bleeding event and number needed to harm

	Cangrelor N=5529 (%)	Clopidogrel N=5527 (%)	Number Needed to Harm
GUSTO severe or moderate	32 (0.58)	20 (0.36)	461
GUSTO severe	11 (0.20)	6 (0.11)	1106
GUSTO moderate	21 (0.38)	14 (0.25)	790
TIMI major or minor	45 (0.81)	17 (0.31)	198
TIMI major	12 (0.22)	6 (0.11)	922
TIMI minor	33 (0.60)	11 (0.20)	251

Reviewer's analysis: rb\nnt.

Our conclusions regarding the benefit risk of cangrelor remain the same as in our original NDA review. The benefit of cangrelor compared to clopidogrel is small, but the risk is smaller. Treating 171 patients prevents one clinically meaningful periprocedural MI. In comparison, treating 1106 patients causes one GUSTO severe bleed, a safety factor of ~ 6.5 fold.[9] Using a less severe bleed to assess benefit risk, such as a GUSTO moderate or TIMI minor bleed still favors the use of cangrelor. (Please see *Section 5 Bleeding Summary* for more discussion on the utility of the bleeding classifications.)

2 Introduction

In 2013 The Medicines Company submitted NDA 204958 for approval to market cangrelor for two indications:

9 GUSTO severe bleed is an intracranial hemorrhage or bleeding resulting in hemodynamic compromise.

1. For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI indication), and
2. To maintain $P2Y_{12}$ inhibition in patients with acute coronary syndromes or patients with stents who are at increased risk of thrombotic events (such as stent thrombosis) when oral $P2Y_{12}$ therapy is interrupted due to surgery (bridging indication).

The Applicant conducted three large outcome trials intended to provide substantial evidence of efficacy and safety for the PCI indication; CHAMPION PCI, CHAMPION PLATFORM, and CHAMPION PHOENIX. All three trials were randomized, double-blind, superiority trials in which patients following coronary angiography were randomized prior to percutaneous coronary intervention to either a) intravenous (IV) cangrelor followed by clopidogrel 600 mg after the 2 hour cangrelor infusion or b) IV placebo + clopidogrel. CHAMPION PCI started 7 months prior to CHAMPION PLATFORM. Both trials were stopped early for futility; however CHAMPION PCI nearly completed enrollment. CHAMPION PHOENIX was designed with knowledge of the first two trials; the Applicant modified the ascertainment of periprocedural myocardial infarction and included ST in the primary endpoint (See ***Table 4.*** See ***Section 7.1*** for the flow of the CHAMPION PHOENIX trial).

Table 4: Summary of CHAMPION Program for the PCI Indication

		PCI	PLATFORM	PHOENIX
Subjects randomized (% of planned enrollment)		8,846 (99%)	5,346 (85%)	11,145 (100%)
Primary endpoint at 48 hours		Death, MI, or IDR	Death, MI, or IDR	Death, MI, IDR, or ST
Outcome of primary analysis, OR (95% CI)		1.05 (0.88, 1.24) p-value=0.59	0.87 (0.71, 1.07) p-value=0.18	0.78 (0.66, 0.93) p-value=0.005
Clopidogrel timing in placebo arm		600 mg immediately before PCI	600 mg after PCI	300 or 600 mg immediately before or after PCI
Population enrolled (%)	Stable angina	15	5	58
	NSTE-ACS	64	95	26
	STEMI	11	excluded	16

The Division of Cardiovascular and Renal Products (Division) and Cardiovascular Advisory Committee (AC) members had a number of issues regarding the approvability and labeling of cangrelor. The AC members voted 2 yes, 7 no, (with 0 abstentions) on the approvability of cangrelor for the PCI indication. The Division issued a Complete Response (CR) letter to the Applicant on 30 April 2014 identifying the reasons for not approving cangrelor at that time.

The Applicant conducted one phase 2 pharmacodynamic study in support of the bridging indication. The AC members voted unanimously against approval of cangrelor for the bridging indication because of the lack of clinical data. The Applicant withdrew its request for a bridging indication, and thus, it is not discussed in this review.

3 List of Issues

The issues raised during the review process and during the AC meeting leading to a complete response letter are listed here:

- Some subcomponents of the primary endpoint in CHAMPION PHOENIX may not represent clinical benefit
- Relevancy of CHAMPION PHOENIX data to current American practice
- General approvability
- Transition from cangrelor to an oral $P2Y_{12}$ antagonist
- Uncertainty about cangrelor utility in patients with stable angina undergoing PCI
- Baseline clinical diagnosis: "derived patient type" vs. investigator assessment at time of enrollment
- Database management

4 Assessment of Issues

4.1 Some subcomponents of the primary endpoint in CHAMPION PHOENIX may not represent clinical benefit

Problem: The PHOENIX trial demonstrated superiority of cangrelor over clopidogrel for the primary endpoint (composite of death, MI, ST, and IDR) in the mITT population (OR 0.78, 95% CI 0.66-0.93, p=0.005). However, it was noted that IPST, a new biomarker included as a secondary endpoint in a protocol amendment, was incorporated post-hoc into the ST component of the primary endpoint. There was no description of IPST in the angiographic core lab charter, and it was not clear from the documents submitted with the NDA how IPST was adjudicated. We recognized that IPST was associated with post procedure ischemic events, perhaps an argument for including them, but it was not clear they were a cause of such events. Investigators were instructed to record the timing of an IPST diagnosis at the end of diagnostic angiography prior to the start of PCI. The Applicant opined that any thrombotic event occurring in the cardiac catheterization laboratory was automatically assigned a diagnosis of IPST. It was not clear whether the angiographic appearance of a thrombosis was due to stent placement or due to the pathophysiology of coronary artery disease.

The FDA reviewers and the AC members questioned the clinical significance of periprocedural myocardial infarction. Periprocedural myocardial infarction was generally based on chemical biomarker elevations in the absence of other signs or symptoms. One of the AC members questioned the benefit risk of cangrelor based on:

1) failure to prevent symptomatic myocardial infarction in the previous failed studies, 2) showing efficacy in lowering the rate of generally asymptomatic elevations in CK-MB, which are not routinely evaluated in clinical practice, and 3) increased bleeding. We also were concerned that attainment of statistical significance favoring cangrelor for the adjudicated primary endpoint may have been an artifact of: 1) Clinical Endpoint Committee (CEC) adjudication rules that led to counting many cases with small increments in CK-MB as periprocedural MIs, and 2) IPST diagnoses defined as any thrombotic event occurring in the catheterization laboratory when all of them were documented to have occurred before the commencement of PCI.

The Applicant was asked to perform a series of sensitivity analyses that modified the primary analysis of PHOENIX by first removing IPST, then removing MIs not meeting the definition of clinically relevant periprocedural MI as defined in the SCAI Consensus document (Moussa 2013), and finally removing both variables. The Applicant was also asked to perform an analysis analogous to the primary analysis, but using site-reported events, defined as death, MIs noted on the checkbox on the MI Case Report Form (CRF), and unplanned revascularization or ST noted on the checkboxes on the Revascularization CRF.

Applicant Information: The Applicant performed the requested sensitivity analyses as shown in ***Table 5***. Removal of IPST still yielded a significant difference between the study groups in favor of cangrelor. Removal of both IPST and MI not meeting the definition of a clinically relevant periprocedural MI also yielded a difference between cangrelor and clopidogrel in favor of cangrelor.

Table 5. CHAMPION PHOENIX Sensitivity analyses of primary endpoint

Endpoints	Cangrelor N=5470 (%)	Clopidogrel N=5469 (%)	OR (95% CI)	Nominal p-value
Death, MI, IDR, ST (primary endpoint)	257 (4.7)	322 (5.9)	0.78 (0.66-0.93)	0.005
Death, SCAI MI, IDR, ARC-ST (primary endpoint excluding IPST and MI not meeting SCAI definition)[1]	79 (1.4)	114 (2.1)	0.69 (0.52-0.92)	0.0110
SCAI MI	53 (1.0)	81 (1.5)	0.65 (0.46-0.92)	0.0149
ARC-ST	12 (0.2)	22 (0.4)	0.54 (0.27-1.10)	0.0858
Death, MI (CK-MB ≥ 10x ULN), IDR, ARC-ST (primary endpoint excluding IPST and MIs with CK-MB < 10xULN)[2]	77 (1.4)	111 (2.0)	0.69 (0.51-0.92)	0.0123
MI (CK-MB ≥ 10x ULN)	50 (0.9)	78 (1.4)	0.64 (0.45-0.91)	0.0128

Source: Applicant's Compete Response document (Table 12) - verified by the Office of Biostatistics
1. SCAI MI defined in *Section 7.1.*
2. Moussa et al, 2013.

The Applicant performed the suggested sensitivity analysis of the primary endpoint by site-reported events and compared the results to CEC adjudicated events as shown in *Table 6.* The site-reported primary endpoint was determined two different ways:

- MI recorded by the site on the MI CRF page; IDR recorded by the site on the Revascularization CRF page; and ST from death, MI, IDR, follow-up, and PCI CRF pages.
- MI recorded by the site on the MI CRF page; unplanned revascularizations recorded by the site on the Revascularization CRF page; and ST recorded by the site on the IDR CRF page.

Table 6. Sensitivity analysis of primary endpoint: site reported events

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Site-Reported Events				
Death/MI/IDR/ST[2]	96/5470 (1.8)	121/5469 (2.2)	0.79 (0.60, 1.03)	0.0862
Death/MI/IDR/ST (IDR eCRF)[3]	94/5470 (1.7)	118/5469 (2.2)	0.79 (0.60, 1.04)	0.0957

[1]Includes ARC-ST and IPST. Adjusted for loading dose and baseline patient status in logistic regression.

[2]Includes MIs recorded by the site on the MI eCRF page, IDR recorded by the site on the Revascularization eCRF page, and ST from death, MI, IDR, Follow-up, and PCI eCRF pages.

[3]Includes MIs recorded by the site on the MI eCRF page, unplanned revascularizations recorded by the site on the Revascularization eCRF page, and ST recorded by the site on the IDR eCRF.

ARC-ST=Academic Research Consortium-stent thrombosis; CI=confidence interval; CK-MB=creatine kinase-myocardial band; IDR=ischemia driven revascularization; MI=myocardial infarction; OR=odds ratio; ST=stent thrombosis; ULN=upper limit of normal.

Source: Applicant's Complete Response Document (Table 15)

The Applicant opined that the results showed no significant difference between the site-reported events and adjudicated events for the comparison between cangrelor and clopidogrel. The odds ratios for adjudicated endpoints and site reported endpoints were identical.

Reviewer Evaluation: The Office of Biostatistics independently confirmed the sensitivity analyses the Applicant provided in ***Table 5***. The results of the sensitivity analyses showed that the 48 hour composite endpoint of death, clinically relevant periprocedural MI (SCAI MI), IDR, and ARC-ST was lower in the cangrelor arm (OR 0.69, 95% CI 0.52-0.92, nominal p-value 0.01).

The Applicant's data showed similar odds ratios between the site-reported and adjudicated 48-hour protocol-defined primary endpoint (***Table 6***). This finding attenuated the concern that the adjudication process biased the results of the trial. The 95% confidence intervals crossed the line of unity for the site reported events.

The Office of Biostatistics performed an independent analysis of the 48 hour primary endpoint as reported by the sites compared to adjudicated endpoints for the ITT population. The results are shown in ***Table 7***. The difference between cangrelor and clopidogrel was evaluated for the entire cohort as well as for subjects presenting with SA, NSTE-ACS and STEMI. The results showed a lower incidence of the primary endpoint in the cangrelor arm compared to the clopidogrel arm for the entire cohort using either site-reported or adjudicated endpoints. This trend was observed for the population presenting with SA and NSTE-ACS. In the STEMI population, the incidence

for the adjudicated primary endpoint was equal in both arms (2.8%), whereas the incidence of site-reported endpoints was slightly higher in the cangrelor arm (2.4%) compared to the clopidogrel arm (2.2%).

Table 7. Site-reported vs. adjudicated 48 hr. primary endpoint analysis

	Adjudicated primary endpoint		Site-reported primary endpoint	
	Clopidogrel	**Cangrelor**	**Clopidogrel**	**Cangrelor**
SA	217/3208 (6.8%)	182/3220 (5.7%)	65/3208 (2.0%)	53/3220 (1.7%)
NSTE-ACS	82/1435 (5.7%)	53/1479 (3.6%)	37/1435 (2.6%)	27/1479 (1.8%)
STEMI	26/921 (2.8%)	25/882 (2.8%)	20/921 (2.2%)	21/882 (2.4%)
all	325/5564 (5.8%)	260/5581 (4.7%)	122/5564 (2.2%)	101/5581 (1.8%)

Source: Office of Biostatistics. Population: ITT.

Conclusion: We believe that cangrelor was demonstrated to be effective when only endpoints whose clinical meaningfulness is undisputed were analyzed. There was no difference in the odds ratios between the adjudicated and site-reported 48 hour primary endpoint.

4.2 Relevance of PHOENIX data to current American Practice

Problem: Uncertainty was expressed about whether or not the data from PHOENIX was relevant to current American practice. The PHOENIX protocol restricted the use of glycoprotein IIb/IIIa receptor antagonists, which was not consistent with either current practice guidelines or practice, although many patients are not given these drugs. Clopidogrel was initiated only at the start of PCI despite a presentation to the CHAMPION-PCI and PLATFORM Executive Committee by the Applicant dated 07 May 2007 stating that clopidogrel must be loaded at least 2 hours before PCI to have an adequate effect. The Applicant was asked to explain why PHOENIX data were relevant to current American practice.

Applicant Information: The Applicant's response to this question was summarized as follows:

- Ad-hoc PCI is a feature of American practice. Ad-hoc PCI is defined as PCI performed at the same session as diagnostic catheterization, compared to staged-PCI where PCI is performed at a subsequent session scheduled after diagnostic angioplasty. The Applicant stated that 63 US sites (41% of all sites enrolling 38% of all subjects) routinely performed ad-hoc PCI.

- Timing of clopidogrel administration is variable and likely due to the absence of firm guidelines.
- Prasugrel was approved by the FDA based on a similar ad-hoc PCI paradigm.
- GP IIb/IIIa receptor antagonist use "upstream" is declining in American practice. Its use as a concomitant medication was excluded in PHOENIX in order to avoid the possibility of additive bleeding.

Reviewer Evaluation:

Ad-hoc PCI:

We agree that ad-hoc PCI is a feature of American practice. It has become the default strategy for treating acute coronary syndrome, and it is the recommended strategy for patients presenting with STEMI and UA/NSTEMI (Blankenship et al, 2013).

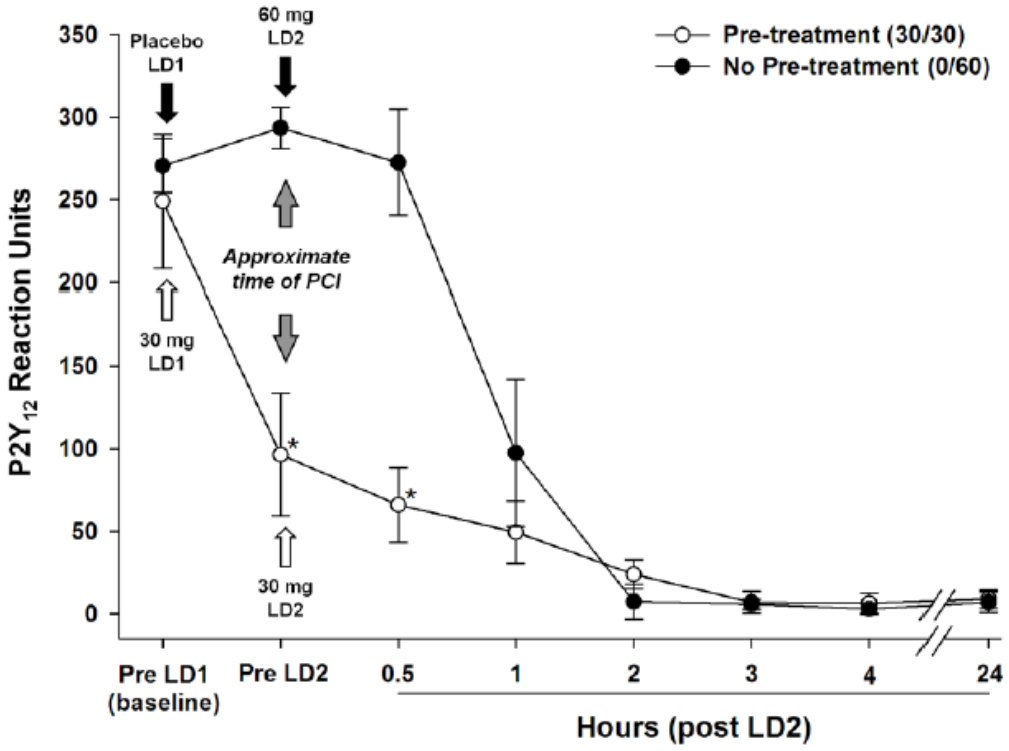
Timing of clopidogrel:

We agree that there are no firm guidelines regarding the optimal timing of $P2Y_{12}$ therapy relative to PCI, and that the timing of clopidogrel in the PHOENIX trial was within the variability of the treatment paradigm.

The ACCF/AHA/SCAI Guideline for PCI (Levine et al, 2011) stated that "the efficacy of clopidogrel remains controversial. Although some studies have suggested that pretreatment with clopidogrel is associated with decreased platelet aggregation and a significantly lower incidence of periprocedural MI after elective PCI, others have suggested no benefit to pretreatment compared with administration of the drug in the catheterization laboratory" (section 5.7.2 of guideline).

A recently published prospective randomized double-blind trial (ACCOAST-PCI) evaluated the effect of prasugrel pre-treatment in patients undergoing PCI for NSTEMI (Montalescot et al, 2014). A total of 4033 subjects were randomized: prasugrel pre-treatment (30 mg upon admission to the hospital, and 30 mg at time of PCI, n=2037) vs. no pre-treatment (60 mg at time of PCI, n=1996). ***Figure 1*** shows the PD profile (Platelet Reaction Units) versus time for the pre-treatment and no-pre-treatment arms. In the pre-treatment arm, the Platelet Reaction Unit was significantly lower than that for the no-pre-treatment arm. ***Figure 2*** shows the cumulative Kaplan-Meyer estimates for key efficacy endpoints (i.e. CV death, MI, or Stroke). The results showed no difference between the arms despite the significant PD effect for the pre-treatment arm. ***Figure 3*** shows the accumulative Kaplan-Meyer estimate for all TIMI Major or Minor bleeding. The results show a significant increase in TIMI bleeding in the pre-treatment group. The expected pharmacodynamic effect of preloading prasugrel demonstrated no enhancement of efficacy but only harm.

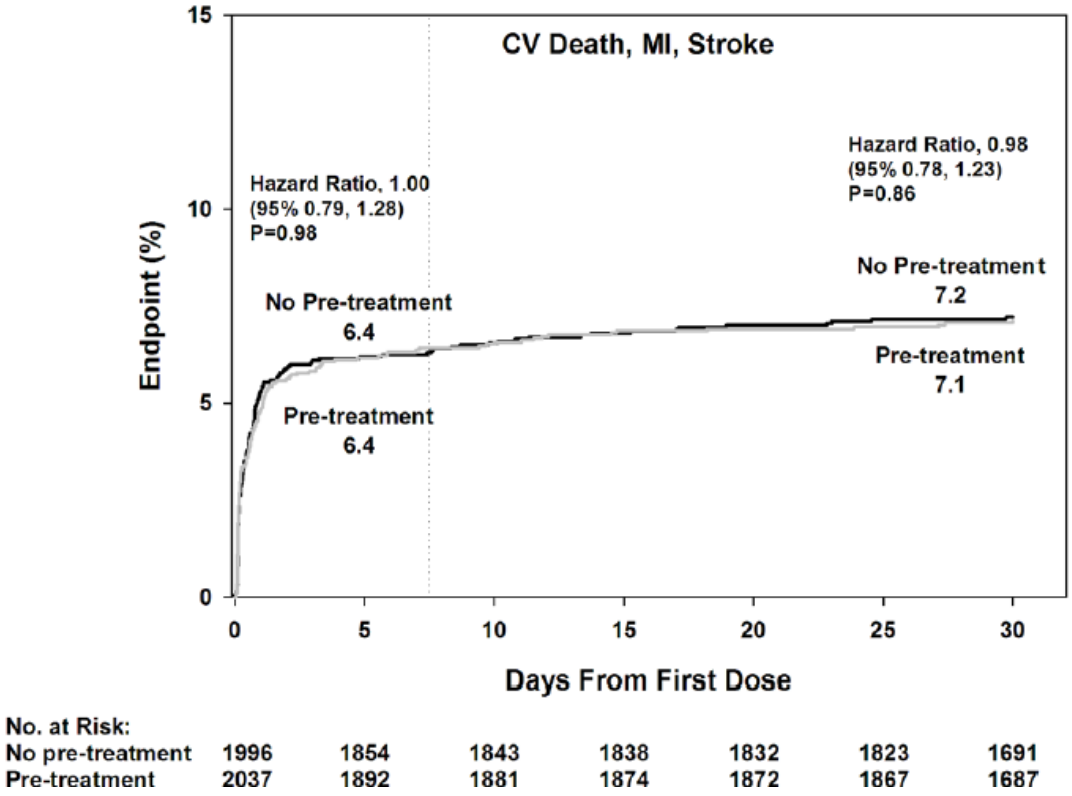
Figure 1. ACCOAST Trial: PD Profile for each study arm



Data presented as median ± SEM. * p<0.05 relative to the No Pre-treatment group. LD – loading dose. Pretreatment=Prasugrel 30 mg/Prasugrel 30 mg; No Pre-treatment=Placebo/Prasugrel 60 mg

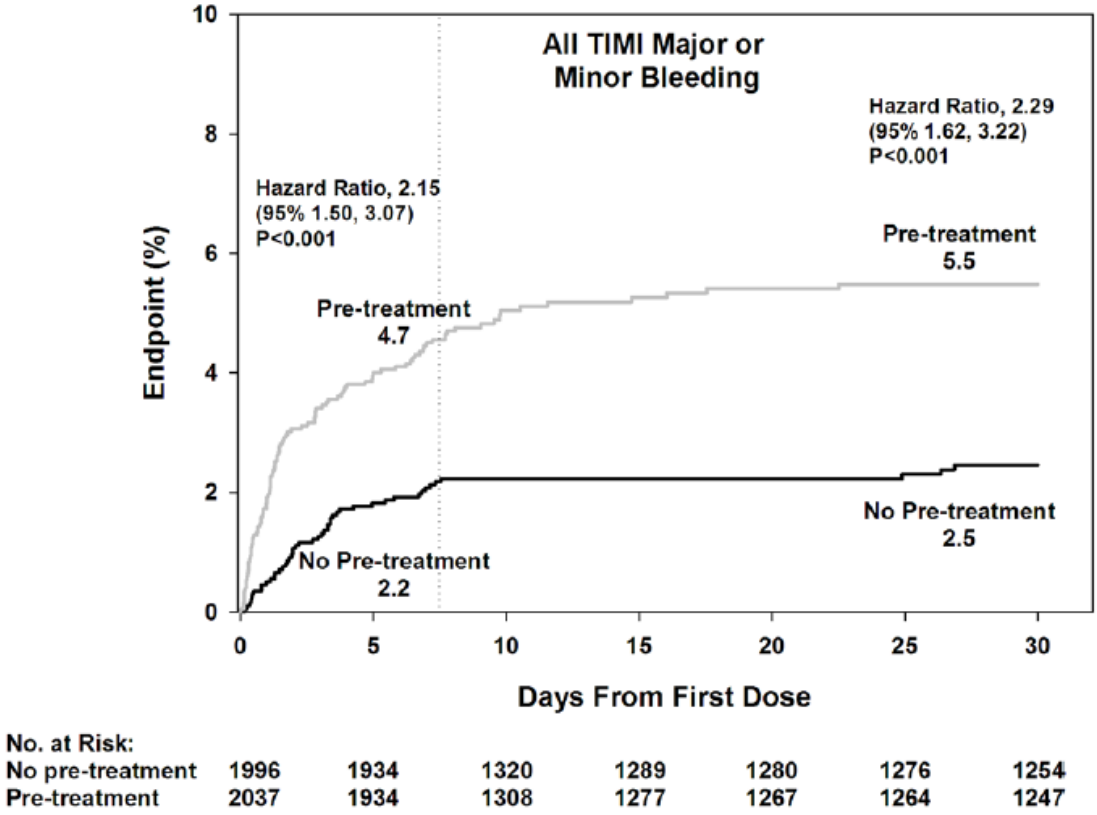
Source: Montalescot et al, 2013-Supplementary Appendix

Figure 2. ACCOAST Trial: Cumulative KM estimates of key study endpoints: CV death, MI, stroke



Source: Montalescot et al, 2013-Supplementary Appendix

Figure 3. ACCOAST Trial: Cumulative KM estimates of key safety endpoints: All TIMI major or minor



Source: Montalescot et al, 2013-Supplementary Appendix

These findings did not support a pre-treatment strategy using a split loading dose of prasugrel in the NSTEMI population. The ACCOAST-PCI trial, the only prospective trial testing the hypothesis that pre-treatment with a $P2Y_{12}$ antagonist is better than treatment at the time of PCI, confirmed that a pre-treatment strategy may not be optimal and that robust evidence is still required to reinforce society-driven practice guidelines (Ibanez & Dangas, 2014).

Use of GP IIb/IIIa receptor antagonists

The guidelines for patients with stable ischemic heart disease (Levine et al, 2011) stated that “in patients undergoing elective PCI with stent implantation treated with unfractionated heparin and adequately treated with clopidogrel, it might be reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high dose bolus tirofiban)”. The Class of Recommendation (COR) and Level of Evidence (LOE) for the use of GP IIb/IIIa receptor antagonists without clopidogrel pretreatment in PCI was COR IIa, LOE A in the STEMI population; COR I, LOE A in

the UA/NSTEMI population, and COR IIa, LOE B in the stable ischemic population. The use of GP IIb/IIIa receptor antagonists with clopidogrel pretreatment was COR IIa, LOE C in the STEMI population; COR IIa, LOE B in the UA/NSTEMI population, and COR IIb, LOE B in the stable ischemic population. Based on the guideline recommendations and supportive evidence from the guideline, the benefit greatly outweighs the risk with high level of evidence for the use of GP IIb/IIIa agents without clopidogrel in patients presenting with STEMI and UA/NSTEMI. The benefit also outweighs the risk when GP IIb/IIIa receptor antagonists are used in concert with clopidogrel pre-treatment although the evidence is limited.

In the CHAMPION PLATFORM and CHAMPION PCI trials, the use of GP IIb/IIIa receptor antagonists (GPI) was originally allowed at the discretion of the investigator. On May 8, 2007, both PCI and PLATFORM protocols were amended to exclude use of GPI within the previous 12 hours prior to enrollment. The use of GPI as an elective concomitant medication was still allowed but the investigators were cautioned that “the use of these agents should be considered carefully based on the anti-platelet effect already provided by the study drug, i.e. clopidogrel 600mg or cangrelor”. In a series of Executive / Steering Committee meetings (September 2007, November 2007, and March 2008), the Applicant reported the results of GPI use in the NSTEMI population at discrete time points during the course of the PLATFORM and PCI trials. These reports are compiled in ***Table 8***. The data shows that following the protocol amendments of CHAMPION PLATFORM and CHAMPION PCI, the number of NSTEMI subjects in PLATFORM increased from 19% to 53% and the use of GPI in NSTEMI subjects decreased from 37% to 12%. Similarly in the PCI trial, the number of NSTEMI subjects increased from 22% to 58% and the use of GPI in NSTEMI subjects decreased from 53% to 35%. In the PHOENIX trial, a total of 380 subjects (153 in the cangrelor arm and 227 in the clopidogrel arm) were administered GPI as bailout medication, representing 3.4% of the ITT population. The data from the antecedent CHAMPION trials suggest that common practice would deploy GPI agents at a much higher incidence than that seen in PHOENIX, as well as in the PCI and PLATFORM trials post-amendment. It is not clear what the outcome of PHOENIX would have been if patients who might have required GPI therapy were enrolled in PHOENIX, especially when the concomitant use of GPI and clopidogrel has been recommended with a COR IIa, LOE B in the UA/NSTEMI population.

Table 8. Use of GP IIb/IIIa receptor antagonists in NSTEMI subjects over time in CHAMPION PCI and CHAMPION PLATFORM

CHAMPION	April 2007	September 2007	November 2007	March 2008
PCI		N= 4338	N= 4684	N=5541
-NSTEMI	22%	43%	45%	58%
-GPI use in NSTEMI	53%	38%	38%	35%
PLATFORM		N=1387	N=1556	
-NSTEMI	19%	34%	38%	53%
-GPI use in NSTEMI	37%	14%	14%	12%

Source: Slide presentations from CHAMPION Executive Committee/Steering Committee Meetings dated March 27, 2007; September 2, 2007; November 3, 2007; March, 2008 (day not specified)

> The Applicant's argument that the use of GP IIb/IIIa receptor antagonists is in decline, and the evidence provided by the Applicant to support this argument, has not been accompanied by any evidence signaling a concern about relative efficacy or safety of this class of antiplatelet drug compared to other classes of antiplatelet drugs.

Conclusion: We believe that ad-hoc PCI is a common feature of American practice. The timing of $P2Y_{12}$ therapy is variable and the guidelines have not provided firm instructions. The only prospective randomized clinical trial testing the hypothesis that pre-treatment of PCI patients with $P2Y_{12}$ inhibitors is more efficacious than treatment at the time of PCI showed no difference in efficacy between prasugrel pre-treatment and prasugrel treatment at the time of PCI in patients presenting with NSTEMI, but a greater safety risk in the pre-treatment arm. The concomitant use of cangrelor with a GP IIb/IIIa agent has not been tested, but combination therapy using clopidogrel and a GP IIb/IIIa agent showed a benefit outweighing risk with limited population studies as a guideline for American practice. Based on previous CHAMPION trials, it appears that if patients who might have required GPI therapy were enrolled in PHOENIX, the rate of use probably would have been much higher and the outcome of the trial might have been different.

4.3 General Approvability

Problem: Concern was expressed about whether the PHOENIX trial could serve as the basis of approval in the setting of two previously failed clinical trials.

Applicant Information: The Applicant argued that CHAMPION-PCI and CHAMPION-PLATFORM, although failed studies, served as the basis for the hypothesis tested in the PHOENIX trial.

Reviewer Evaluation: Post-hoc analyses of these two failed studies showed a potential utility for cangrelor in preventing periprocedural myocardial infarction. The consequent hypothesis was proven in the PHOENIX trial. We do not consider the failed studies to offset the successful PHOENIX trial because the hypotheses and endpoints in PHOENIX were different from the two failed studies. Clopidogrel, as an approved $P2Y_{12}$ agent, was an appropriate active comparator. An established basis for approvability from a single Phase 3 trial, a very small p-value, was met. The outcome in PHOENIX was significant with a p value of 0.0049. Following the exploratory sensitivity analysis for outcomes whose clinical relevance is not in dispute, the results were still significant with a p value of 0.0123.

Conclusion: The PHOENIX study as a stand-alone trial was sufficient to warrant approval of cangrelor in patients undergoing PCI for the prevention of periprocedural MI and stent thrombosis.

4.4 Transition from cangrelor to an oral $P2Y_{12}$ agent

Problem: Concern was expressed that there was a window of pharmacodynamic vulnerability between the time when cangrelor was discontinued and the time when there was a therapeutic effect of clopidogrel, which was started when cangrelor was stopped. Clopidogrel took at least 2 hours to reach therapeutic effect, even if the loading was doubled to 600 mg. Therefore subjects in PHOENIX had a period of at least 2 hours after cessation of cangrelor infusion during which platelets were inadequately inhibited. This indicated that use of cangrelor delays, but does not eliminate, a time-period during which clopidogrel is ineffective. The question therefore is what the consequence of the later delay is.

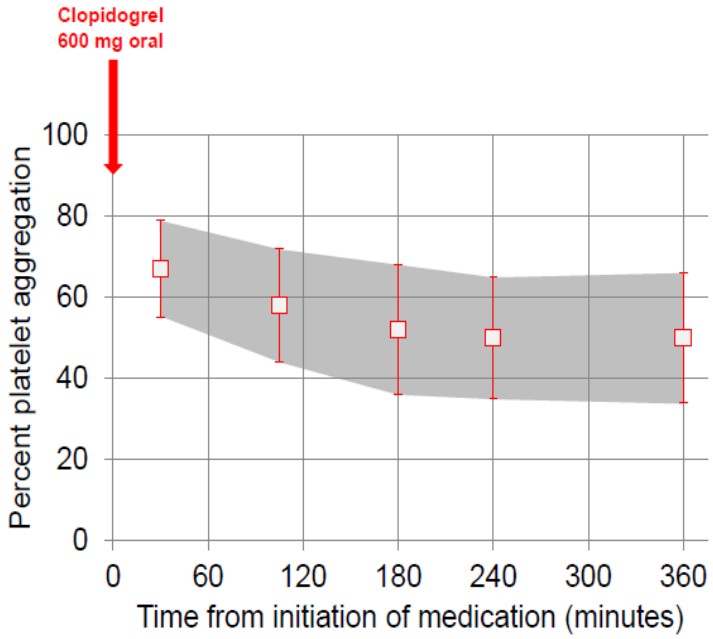
Applicant Information: The Applicant responded by opining that "when clopidogrel is loaded at the end of the cangrelor infusion as proposed, antiplatelet effects are not anticipated to be below the desirable level for very long-if at all-compared to loading clopidogrel at the time of PCI". The Applicant provided the following additional arguments:

- Even at 2-4 hours, clopidogrel effects are not fully developed. Studies among patients undergoing coronary artery stenting and given clopidogrel 600 mg orally have shown that platelet aggregation in response to 20 uM ADP stimulation ex-vivo ranged from 30% (SD 10%)--52% (SD 16%) at 2-4 hours. The Applicant provided a figure that is reproduced here as ***Figure 4***. This figure shows platelet aggregation ranging from approximately 70% to 50% between 30 minutes to 360 minutes following a clopidogrel loading dose of 600 mg.
- Administration of clopidogrel while cangrelor is being infused may be associated with diminished clopidogrel effects consequent to pharmacodynamic interactions. However, administration of clopidogrel after the end of a cangrelor infusion does not lead to clinically important loss of effects. Following a 2-hour infusion of

cangrelor during which platelet aggregation was effectively eliminated, and a post-infusion clopidogrel 600mg load, platelet aggregation in response to 20 uM ADP stimulation ex-vivo ranged from 26% to 58% at 2-4 hours post cessation of cangrelor infusion and clopidogrel load (***Figure 5***). However, there was a window of pharmacodynamic vulnerability where platelet aggregation rose to approximately 60% between 2-3 hours post initiation of cangrelor (approximately 1 hour post cessation of cangrelor). Platelet aggregation returned to 20% at 6 hours post initiation of cangrelor (4 hours post-termination of cangrelor). The Applicant provided several arguments regarding this apparent window of pharmacodynamic vulnerability (ref: Applicant's Response Document section 5.5): "Any differences during the 2-4 hour period of transition between platelet inhibition on clopidogrel after cangrelor compared with platelet inhibition on clopidogrel started immediately are (a) modest and not clinically important (b) of short duration (< 1 hour), (c) fall within the expected wide variability of antiplatelet effect at 2-4 hours normally observed among patients dosed with clopidogrel 600 mg orally at the time of PCI and (d) occur at a time of lower thrombotic risk relative to the peri-PCI period".

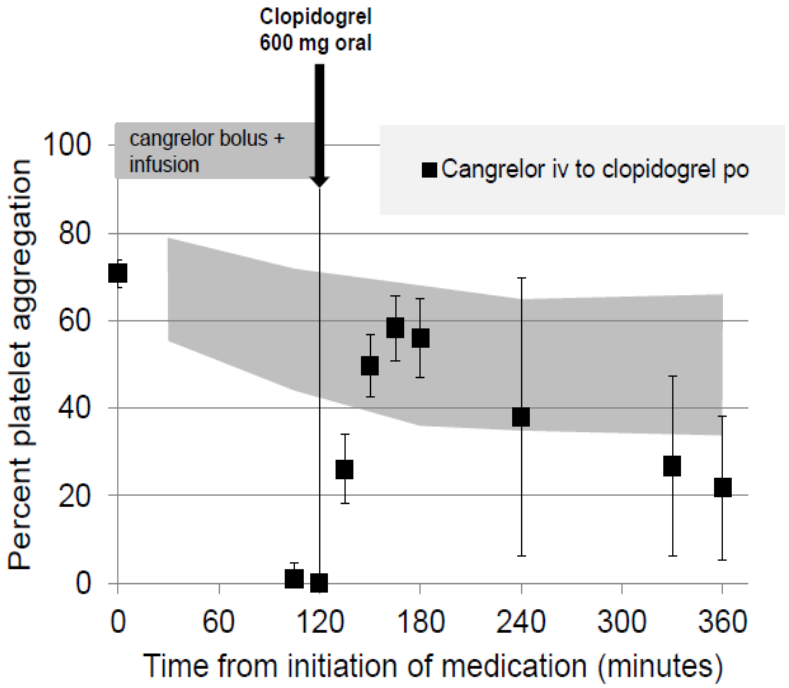
- Most events occurred within the initial 6 hours post randomization in PHOENIX (CSR, Table 10 Landmark Analysis). Further analysis by the Applicant showed that most of these 6-hour post randomization events occurred within the first 2 hours post randomization (see Applicant's Complete Response Figure 6) at a time when cangrelor would be effective compared to clopidogrel. The 2-4 hour infusion of cangrelor therefore provided coverage during the most important risk period.
- Transitions to other P_2Y_{12} inhibitors:
    - Prasugrel also exhibited an interaction with cangrelor but if given 30 minutes before the end of cangrelor infusion, platelet reactivity briefly increased to 49%, thus minimizing platelet reactivation (study MDCO-CAN-13-02).
    - Ticagrelor did not interact with cangrelor. Platelet function in the cangrelor-ticagrelor transition period was reportedly less than 20% (study MDCO-CAN 12-13).

Figure 4. Platelet aggregation ex-vivo after clopidogrel 600 mg given for PCI



Source: Applicant's Complete Response Document (Figure 3)

Figure 5. Platelet aggregation with cangrelor followed by clopidogrel 600 mg



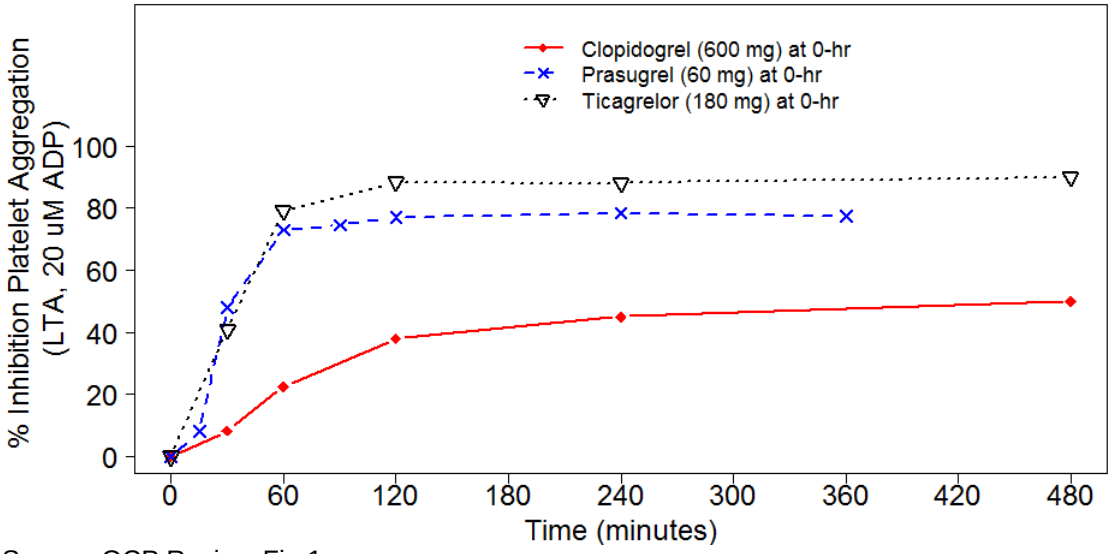
Source: Applicant's Complete Response Document (Figure 4)

Reviewer Evaluation:

Transition Data

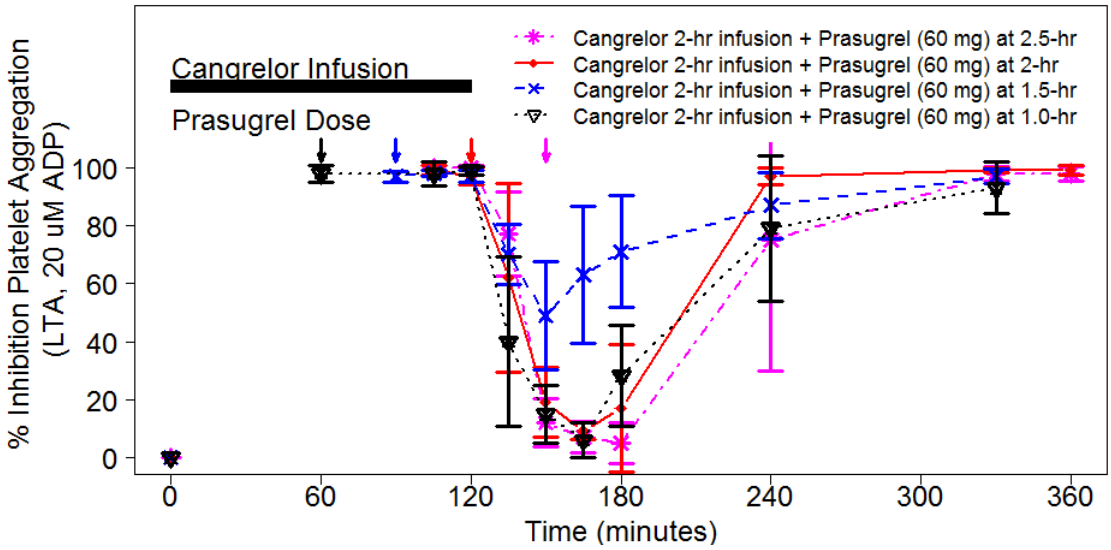
The Office of Clinical Pharmacology performed a transition analysis assessing inhibition of platelet aggregation as a function of time when cangrelor was replaced by various $P2Y_{12}$ agents. ***Figure 6*** shows the percent inhibition of platelet aggregation (IPA) for loading doses of clopidogrel, prasugrel, and ticagrelor as a function of time. The IPA-time profile for prasugrel and ticagrelor are similar where each had a higher IPA compared to clopidogrel for all time points. ***Figure 7*** shows cangrelor→prasugrel transition data for a prasugrel 60 mg load provided at various time points after the start of a 2-hour cangrelor infusion. The data suggested that the loss of IPA during the cangrelor→prasugrel transition was minimized when prasugrel 60 mg load was provided 1.5 hours after the start of the 2-hour cangrelor infusion (i.e. 30 minutes before the end of the cangrelor infusion). ***Figure 8*** shows cangrelor→ticagrelor transition data for ticagrelor 180 mg provided 0.5 hours and 1.25 hours after the start of a cangrelor 2-hour infusion. The data suggested an overlapping loss of IPA 30 minutes after the end of cangrelor infusion (from > 90% IPA to 60% IPA when ticagrelor was given 85 minutes after the start of the 2-hour cangrelor infusion; from > 90% IPA to ≈ 80% IPA when ticagrelor was given 30 minutes after the start of cangrelor infusion). ***Figure 9*** shows the combined time-course of IPA for clopidogrel, prasugrel, and ticagrelor using the OCP recommended transition strategies for each oral $P2Y_{12}$ agent. The data shows that the OCP recommendation of ticagrelor 180 mg administered 30 minutes after the start of a 2-hour cangrelor infusion minimizes the loss of IPA. The OCP also recommended prasugrel 60 mg immediately after the end of a 2-hour cangrelor infusion as well as clopidogrel 600 mg immediately after the end of a 2-hour cangrelor infusion. However, the use of prasugrel or clopidogrel as the transition agent showed a significant loss of IPA for approximately 2 hours after the end of cangrelor infusion. We believe that ticagrelor should be the preferred agent of choice when transitioning from cangrelor to an oral $P2Y_{12}$ agent. However, clinical outcome data are not available to assess bleeding risk for this transition strategy.

Figure 6. Percent Inhibition of platelet aggregation for clopidogrel, prasugrel and ticagrelor loading doses



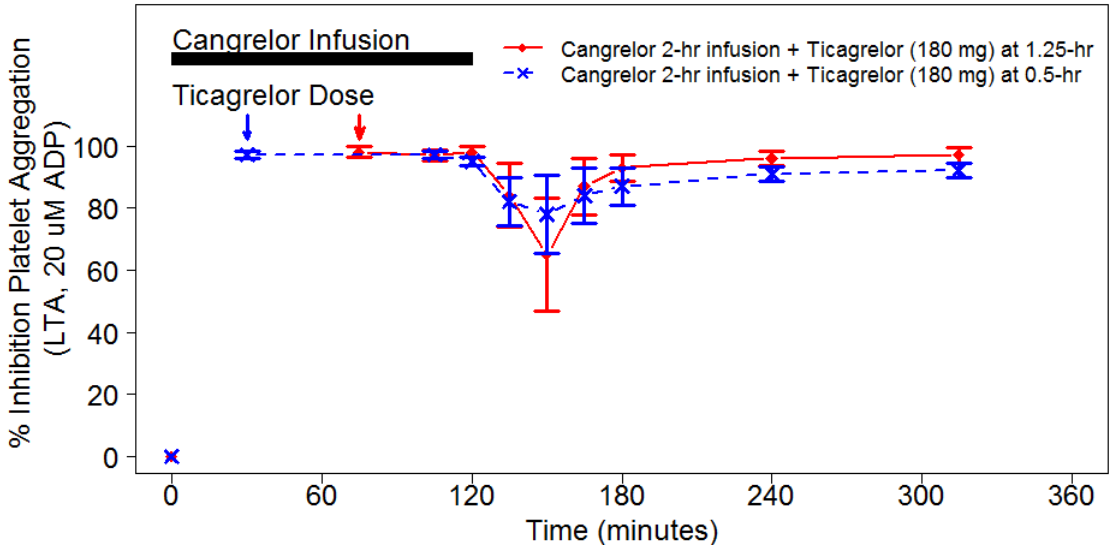
Source: OCP Review-Fig 1

Figure 7. Percent inhibition of platelet aggregation for cangrelor and transition to prasugrel at various times from start of cangrelor infusion



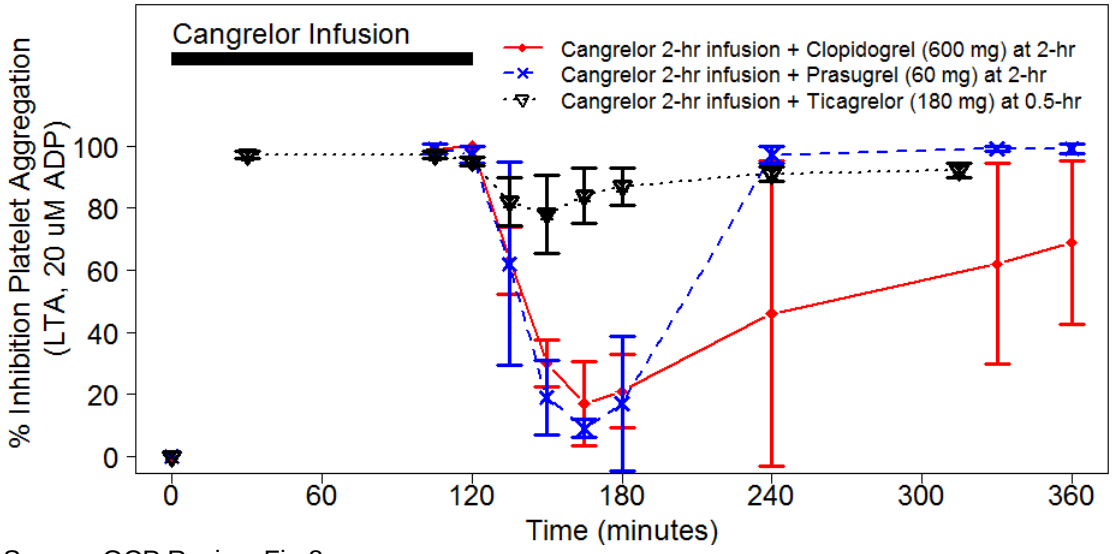
Source: OCP Review-Fig 4

Figure 8. Percent inhibition of platelet aggregation for cangrelor and transition to ticagrelor at various times from the start of cangrelor infusion



Source: OCP Review-Fig 6

Figure 9. Time-course of antiplatelet effect with recommended transition strategies



Source: OCP Review-Fig 8

Clinical Relevance of the Pharmacodynamic Window of Vulnerability

The Office of Biostatistics verified the Applicant's re-evaluation of the landmark analysis using a primary endpoint that excluded IPST and using a more conservative definition of MI (SCAI-MI). The largest separation between the arms of PHOENIX occurred in the initial 2 hours of treatment. The Office of Biostatistics noted that among the 138 endpoints (death, SCAI-MI, IDR, ARC-ST), 41 events (25 in the clopidogrel arm and 16 in the cangrelor arm) occurred within 2 minutes from infusion of the study drug. It is not clear how a periprocedural MI could be diagnosed on the basis of a CK-MB rise 2 minutes into the infusion of study drug when PCI has likely just commenced. The amount of time required for CK-MB to rise would imply that the MI occurred prior to catheterization laboratory entry. If a periprocedural MI occurred, it is expected that the CK-MB would begin rising at the time of PCI, with peaks occurring post-PCI. Therefore, while the transition from cangrelor to an oral $P2Y_{12}$ agent is taking place, the patient might be sustaining a periprocedural MI when platelet reactivation is simultaneously occurring. In order to minimize the probability of post-PCI cardiac adverse events, the question remains as to whether it is necessary to maintain continued adequate inhibition of platelet aggregation (i.e. above 80%) during the transition period, or whether a transient 2-4 hour time period of empirical pharmacodynamic vulnerability is allowable because it poses a negligible clinical risk to the patient. In order to ensure complete coverage post-PCI, pre-treatment loading with a $P2Y_{12}$ agent might be preferable, thereby obviating the utility of cangrelor. The Applicant argued that the 2-4 hour period of inadequate platelet inhibition was similar between clopidogrel after cangrelor and clopidogrel 600 mg started at the time of PCI. The approval of cangrelor should not rest on this argument in a setting where pre-PCI treatment with clopidogrel or ticagrelor is within the practice paradigm.

Conclusion: The use of cangrelor produced a window of pharmacodynamic vulnerability but its clinical relevance has not been established.

4.5 Uncertainty about cangrelor utility in patients with stable angina undergoing PCI

Problem: Uncertainty was expressed over the utility of cangrelor in patients with SA undergoing PCI. These patients could be preloaded with a $P2Y_{12}$ receptor inhibitor before coronary angiography. This would avoid the approximately 2-hour post-PCI decrease in platelet inhibition that occurs after administration of cangrelor followed by clopidogrel. If cangrelor were to be approved, it is not clear which patients with SA could be given clopidogrel only when PCI is initiated, the population in which an effect has been shown rather than before PCI. The Applicant was asked to explain why they believe the data from PHOENIX support use of cangrelor as an adjunct to PCI in patients with SA.

Applicant Information: The Applicant reiterated that cangrelor can be useful in the ad-hoc setting where $P2Y_{12}$ receptor inhibitor was not administered prior to angiography.

Reviewer Evaluation: We acknowledge variability in American clinical practice. In patients undergoing PCI, there are clinical scenarios where a delay in the use of a $P2Y_{12}$ receptor inhibitor until the time of PCI is warranted. Two such scenarios are: 1) ad-hoc PCI in the absence of antecedent $P2Y_{12}$ receptor inhibitor treatment, and 2) delineation of coronary anatomy in order to make a clinical decision prior to giving a $P2Y_{12}$ receptor inhibitor.

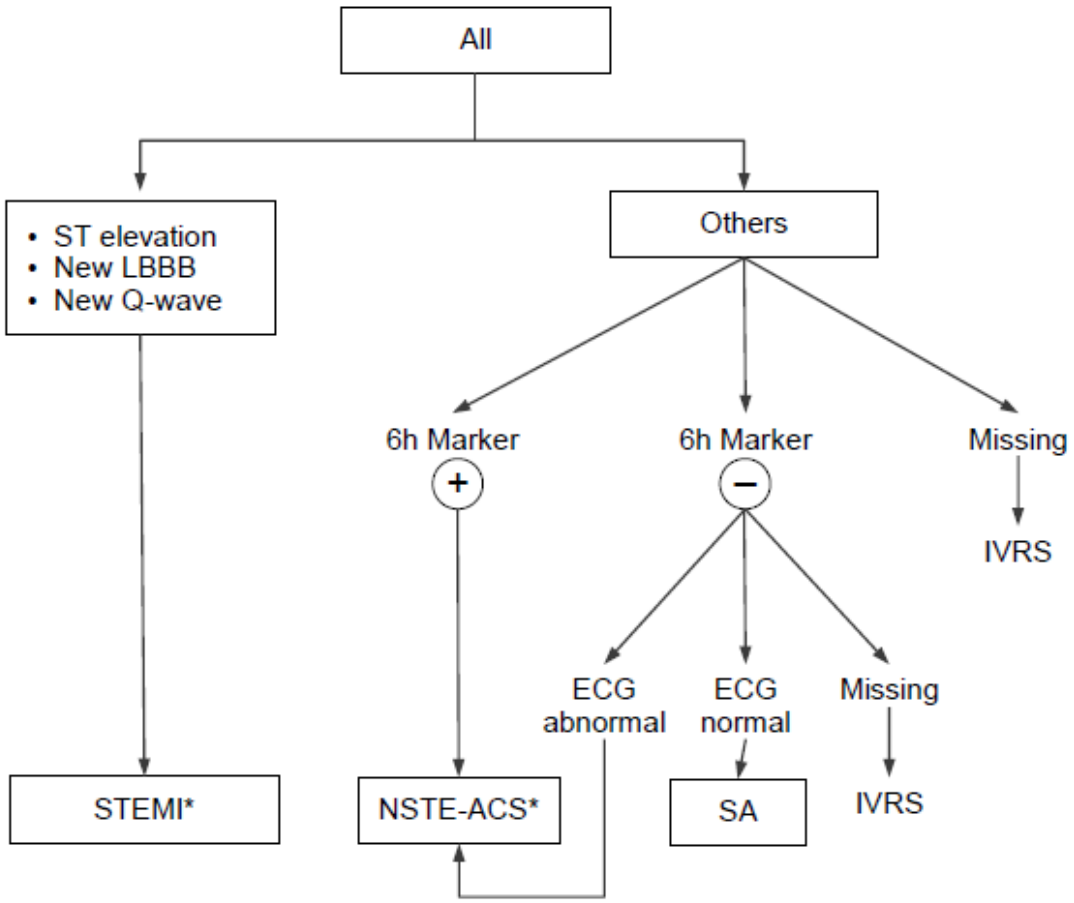
Conclusion: Cangrelor has utility in the clinical setting where patients are not pretreated with $P2Y_{12}$ receptor inhibitor: ad-hoc PCI in the absence of antecedent $P2Y_{12}$ receptor inhibitor treatment, and clinical scenarios where knowledge of coronary anatomy is desired prior to treatment.

4.6 Baseline Clinical Presentation: Derived Patient Type vs Investigator Diagnosis

Problem: After database lock the Applicant defined a “derived patient type”. Upon query, this term was used as a baseline diagnosis of subjects randomized to PHOENIX (i.e. SA, NSTE-ACS, STEMI), based on an algorithm which partly included information that was obtained after the patient’s initial presentation. The derived patient type algorithm resulted in altering the investigators’ initial diagnosis at the time of enrollment without the investigator’s knowledge. The purpose of the derived patient type algorithm was not clearly explained in the original submission, as well as the meaning of the derived patient type and the justification for ignoring the investigators’ original diagnosis. In clinical practice, the decision to prescribe antiplatelet therapy would customarily be based on the clinical impression at the time of diagnosis. The derived patient type algorithm served to incorporate post hoc information that the prescribing physician would not ordinarily have at the time of making an initial clinical judgment. In practice, prescribers would likely have similar data as the investigators had at the time of randomization. Thus, the initial baseline diagnosis as per investigator judgment rather than the Applicant’s diagnosis from the derived patient type algorithm would be the most useful information on which to base prescription instructions. Furthermore, the algorithm was designed and executed after unblinding, raising the possibility of bias when deploying the patient derived type algorithm. The Applicant was asked to provide an exact and detailed description of the process, including when and why the Applicant decided it was necessary to deploy it, the calendar dates during which it was performed, and the name of the group or groups responsible for performing it. In addition, the Applicant was asked to provide a tabular data-set that listed all subjects for whom the clinical presentation entered into the IVRS differed from the results of the derived type algorithm.

Applicant Information: The Applicant described the algorithm used to change the baseline diagnosis of enrolled subjects and is illustrated in ***Figure 10***. After database lock, the program algorithm searched the database for cardiac markers and ECG results. Based on the data, the subject was re-assigned a baseline clinical diagnosis. If data were missing, the algorithm defaulted to the investigator's clinical baseline diagnosis retrieved from the IVRS.

Figure 10. Algorithm for derived patient type using baseline eCRF data



*UDMI definitions (Thygessen)

Source: Applicant's Complete Response Document (Figure 11) - confirmed by the Office of Biostatistics

The Applicant explained the reasons for the difference between site-reported and Applicant-derived clinical presentations as shown in ***Table 9***. In those instances where the site-reported diagnosis was NSTE-ACS, subjects who maintained normal biomarkers within 6 hours of randomization were reclassified as SA. In those instances where the site-reported diagnosis was SA, the development of abnormal biomarkers or

ST segment depression indicative of ischemia during screening resulted in a reclassification to NSTE-ACS. Subjects with a site-reported diagnosis of SA, who developed a new Q-wave or new Left Bundle Branch Block (LBBB) or ST-segment elevation during screening, were reclassified as STEMI. Subjects with a site-reported diagnosis of STEMI were reclassified as SA if ECG criteria for STEMI were not met and there were with normal biomarkers within 6 hours of randomization.

Table 9. Changes in baseline diagnosis from investigator (or IVRS) to derived patient type

Clinical Presentation/ Patient Type				
IVRS	**eCRF Derived**	**Reason for Difference**	**No. of Patients**	**% of N N=10,942**
NSTE-ACS	SA	Normal BL biomarkers within 6 hours of randomization	864	7.9
SA	NSTE-ACS	Abnormal BL biomarkers within 6 hours of randomization	583	5.3
SA	NSTE-ACS	ST segment depression or Other ECG abnormality indicative of ischemia during screening	397	3.6
NSTE-ACS	STEMI	New Q wave, or new LBBB or ST segment elevation during screening	229	2.1
SA	STEMI	New Q wave, or new LBBB or ST segment elevation during screening	101	0.9
STEMI	NSTE-ACS	ECG criteria for STEMI not met and abnormal BL Biomarker within 6 hours of randomization or ST segment depression of other ECG abnormality during screening	24	0.2
STEMI	Stable	ECG criteria for STEMI not met and normal BL biomarkers within 6 hours of randomization	6	0.05

BL=baseline; ECG=electrocardiogram; LBBB=left bundle branch block; NSTE-ACS: non-ST segment elevation-acute coronary syndrome; STEMI=ST segment elevation myocardial infarction.
Source: Applicant's Complete Response Document (Table 18)

The Applicant agreed with our concerns and elected to forgo the derived patient type algorithm in favor of the investigators' baseline diagnosis at the time of randomization.

Reviewer Evaluation: The Office of Biostatistics reproduced the Applicant's derived patient type algorithm and shown in ***Table 10***. The results matched that of the Applicant.

Table 10. Investigator diagnosis vs. derived patient type

		site-reported patient type		
		Stable Angina	NSTE-ACS	STEMI
Derived patient type	Stable Angina	5347	864	6
	NSTE-ACS	980	1821	24
	STEMI	101	229	1773

Source: Statistical Review and Evaluation Addendum (Reviewer's Analysis, Table 4)

Results for the primary endpoint using the derived patient type algorithm for the baseline diagnosis are shown on ***Table 11***. Similarly, results for the primary endpoint using the site-reported database are shown on ***Table 12***. When using the Applicant's algorithm, the odds ratio for the adjudicated primary endpoint favored cangrelor for all clinical presentations, and was significant for subjects with SA. For site-reported baseline diagnoses, the odds ratio for the adjudicated primary endpoint favored clopidogrel in subjects with STEMI, but significantly favored cangrelor in subjects with NSTE-ACS and trended in favor of cangrelor in subjects with SA. The pathophysiology of coronary artery disease is common to all clinical presentations. It is therefore unlikely that cangrelor would be effective only in the NSTE-ACS population but not in patients with SA or STEMI. Notably, there were relatively few endpoint events in the patients with STEMI (22 and 23 in the cangrelor and clopidogrel arms, respectively).

Table 11. Primary endpoint analysis by derived patient type

	cangrelor			Clopidogrel				
	N	event	%	N	event	%	OR	95% CI
stable angina	3120	181	5.8	3018	222	7.4	0.78	(0.63, 0.95)
UA/NSTEMI	1389	49	3.5	1421	62	4.4	0.8	(0.55, 1.18)
STEMI	961	27	2.8	1030	38	3.7	0.76	(0.46, 1.25)

Source: Statistical Review and Evaluation Addendum (Reviewer's Analysis, Table 2)

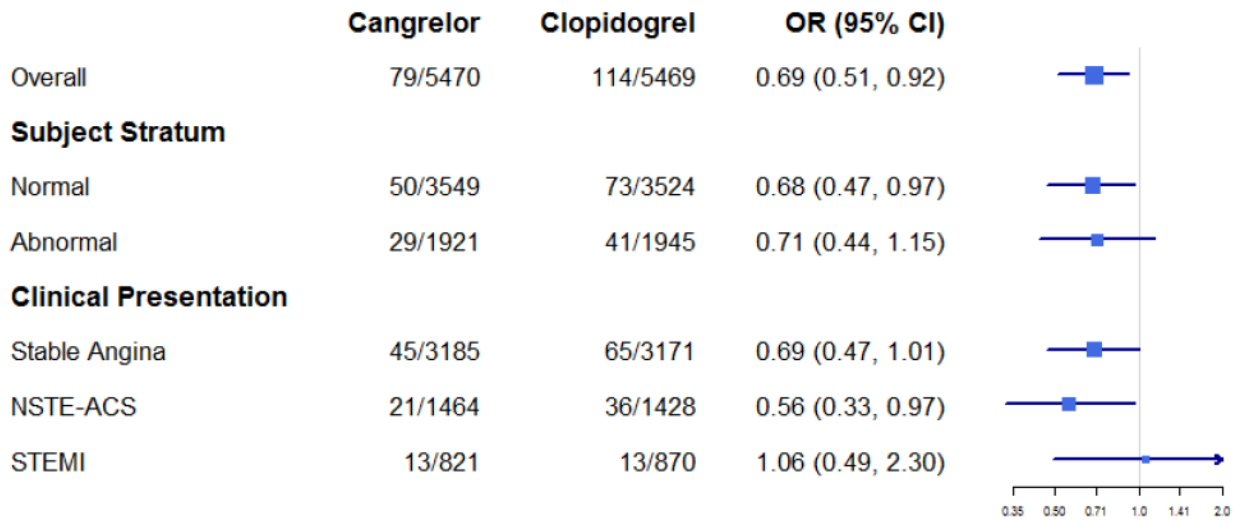
Table 12. Primary endpoint analysis by clinical presentation as assessed by the investigator at the time of enrollment

	cangrelor			Clopidogrel				
	N	event	%	N	event	%	OR	95% CI
stable angina	3185	182	5.7	3171	217	6.8	0.83	(0.67, 1.01)
UA/NSTEMI	1464	53	3.6	1428	82	5.7	0.62	(0.43,0.88)
STEMI	821	22	2.7	870	23	2.6	1.01	(0.56,1.83)

Source: Statistical Review and Evaluation Addendum (Reviewer's Analysis, Table 3)

The Office of Biostatistics created a Forest Plot using the investigators' baseline diagnosis. The results for the endpoint of death, MI (CK-MB ≥ 10x ULN), IDR, and ARC-ST were sub-grouped by baseline diagnosis and is shown in ***Figure 11***. Consistent with our results, the reported OR (1.06) subtended the line of unity when using the investigators' baseline diagnosis of STEMI. When using the derived patient diagnosis, the OR (0.76) favored cangrelor for patients with STEMI. In both cases, the 95% CI crossed the line of unity, thereby making these results not significant. The Forest plot shows the overall benefit of cangrelor for clinically relevant endpoints. The subgroups classified as "normal" (i.e. SA and asymptomatic ACS) or "abnormal" (symptomatic ACS and STEMI) did not reach significance, but did trend in favor of cangrelor.

Figure 11. Forest plot for subgroup analysis of Death / SCAI MI / IDR / ARC-ST at 48 hours by baseline stratum and IVRS clinical presentation



Source: The Office of Biostatistics

Conclusion: There was no overall significant difference in outcome between the patient derived type and investigators' baseline diagnoses. The difference in the OR for STEMI between the derived patient algorithm baseline diagnosis and the investigator baseline

diagnosis was not significant because of the wide confidence intervals crossing the line of unity for each OR estimate. The pathophysiology which subtends the spectrum of coronary artery disease (SA, NSTE-ACS, and STEMI) makes it unlikely that cangrelor would be effective in only one subgroup. The Applicant agreed to use the investigator baseline clinical diagnosis in lieu of the derived patient type algorithm.

4.7 Database Management

Problem: The Applicant unlocked the database to incorporate missing concomitant anticoagulation medication. This involved 553 subjects from 84 sites. The Applicant was asked to provide a detailed description of their database unlocking process and explain the root cause of missing key data.

Applicant Information: The Applicant provided relevant documentation supporting the database unlocking process. The Applicant explained the cause of missing information: transcription error, unfamiliarity with drug names, and site-specific SOP violations.

Reviewer Evaluation: The Office of Scientific Investigation (OSI) conducted a review and determined that the data was acceptable in support of the claimed indication.

Conclusion: The questions about database unlocking have been answered, and there are no issues about database unlocking.

5 Bleeding Summary

The reader should refer to the original clinical review for a complete discussion of the safety findings. This review presents the overall findings of the primary adverse event, major bleeding (see ***Table 13***). There were more bleeds on cangrelor (15.5%) compared to clopidogrel (10.9%); this was true overall as well as within each bleeding classification. The primary safety endpoint was the incidence of GUSTO severe bleeding (intracranial hemorrhage or bleeding resulting in hemodynamic compromise) (see ***Appendices Table 14*** for bleeding definitions). The incidence of a GUSTO or TIMI bleed was less than 1% in each treatment arm with the risk of a GUSTO bleed ranging from 50-83% higher, and the risk of a TIMI bleed being 2-3 fold higher on cangrelor compared to clopidogrel. The incidence of ACUITY major bleeding was higher than either GUSTO or TIMI classifications. This was primarily because of access site hemorrhages and hematomas which are part of the ACUITY major definition.

Table 13. CHAMPION PHOENIX Non-CABG bleeding classification at 48 hours

	Cangrelor N=5529		Clopidogrel N=5527		Cangrelor vs. Clopidogrel	
	n	(%)	n	(%)	OR	(95% CI)
Non CABG bleeds	857	(15.5)	602	(10.9)	1.50	(1.34, 1.68)
GUSTO						
Severe or Moderate	32	(0.6)	20	(0.4)	1.60	(0.92, 2.81)
Severe	11	(0.2)	6	(0.1)	1.83	(0.68, 4.96)
Moderate	21	(0.4)	14	(0.3)	1.50	(0.76, 2.96)
Mild	825	(14.9)	582	(10.5)	1.49	(1.33, 1.67)
TIMI						
Major or Minor	45	(0.8)	17	(0.3)	2.66	(1.52, 4.65)
Major	12	(0.2)	6	(0.1)	2.00	(0.75, 5.34)
Minor	33	(0.6)	11	(0.2)	3.01	(1.52, 5.96)
Acuity						
Major	249	(4.5)	145	(2.6)	1.75	(1.42, 2.16)

Reviewer code: bleed\resub\primary safety. Applicant's datasets: raw\bld, iss\fda_bld, iss lab

Reviewer comment 1: Which bleeding classification should be used for the assessment of safety? Perhaps that is a matter of preference and so three classifications are included in this review. It is the reviewer's belief that the GUSTO severe and moderate are more clinically driven (there are no lab values in its definition) than TIMI major or minor (includes a hemoglobin change). Since both are widely used, the reviewer includes both in this review. The ACUITY major definition includes access site bleeding and hematomas, and in the CHAMPION PHOENIX trial this was the majority of the reason for the ACUITY major bleeds. Since most of the other reasons for an ACUITY major bleed were captured in the GUSTO and TIMI classifications, ACUITY major bleeds were not considered in the reviewer's benefit risk analyses. (See **Section 1.2** *for more discussion on the utility of the bleeding classifications).*

Reviewer comment 2: There were differences between the reviewer's and the applicant's initial report of major bleeds (with generally excess bleeds in the reviewer's analysis). The bleeding risk and the differences between the reviewer's and the applicant's numbers did not preclude the approval of cangrelor in 2014, but it was a

topic of discussion at the AC meeting. After the AC meeting, the Applicant and the reviewer thoroughly discussed the reasons for the differences, agreed on the interpretation of published bleeding classifications, and independently reviewed the data again. ***Table 13*** *is the result of the review, and it should replace Table 59 in the original clinical review.*

Because the incidence of major bleeding is low, subgroup analysis within each classification is unlikely to produce any meaningful results. However, it was done for the combined GUSTO moderate or severe bleeds (even though the combined incidence was less than 1% in each arm). Although the numbers are small, females and patients < 75 years old tended to be at greater risk of bleeding with cangrelor compared to clopidogrel.

6 Summary

Cangrelor was still effective when only endpoints whose clinical meaningfulness is undisputed were analyzed (nominal p-value = 0.0123). The PHOENIX study as a stand-alone trial was sufficient to warrant approval of cangrelor for the prevention of periprocedural MI and stent thrombosis in patients undergoing PCI.

Ad-hoc PCI is a common feature of American practice. Cangrelor has utility in the ad-hoc PCI setting where $P2Y_{12}$ receptor inhibitor was not administered prior to angiography.

The timing of $P2Y_{12}$ therapy is variable and the guidelines have not provided firm evidence of optimal timing. The only prospective randomized clinical trial testing the hypothesis that pre-treatment of PCI patients with $P2Y_{12}$ inhibitors is more efficacious than treatment at the time of PCI showed no difference in efficacy between prasugrel pre-treatment and prasugrel treatment at the time of PCI, but a greater safety risk in the pre-treatment arm. The concomitant use of cangrelor with a GP IIb/IIIa agent has not been tested, but combination therapy using clopidogrel and a GP IIb/IIIa agent showed the benefit outweighing the risk with limited population studies as a guideline for American practice. Based on previous CHAMPION trials, it appears that if subjects likely to require GP IIb/IIIa antagonists were enrolled in PHOENIX, the rate of use probably would have been much higher and the outcome of the trial might have been different.

The use of cangrelor produced a window of pharmacodynamic vulnerability that could be clinically relevant but did not seem to abort results in PHOENIX.

Our conclusions regarding the benefit risk of cangrelor remain the same as in our original NDA review. The benefit of cangrelor compared to clopidogrel is small, but the risk is smaller. Treating 171 patients prevents one clinically meaningful periprocedural MI. In comparison, treating 1106 patients causes one GUSTO severe bleed, a safety

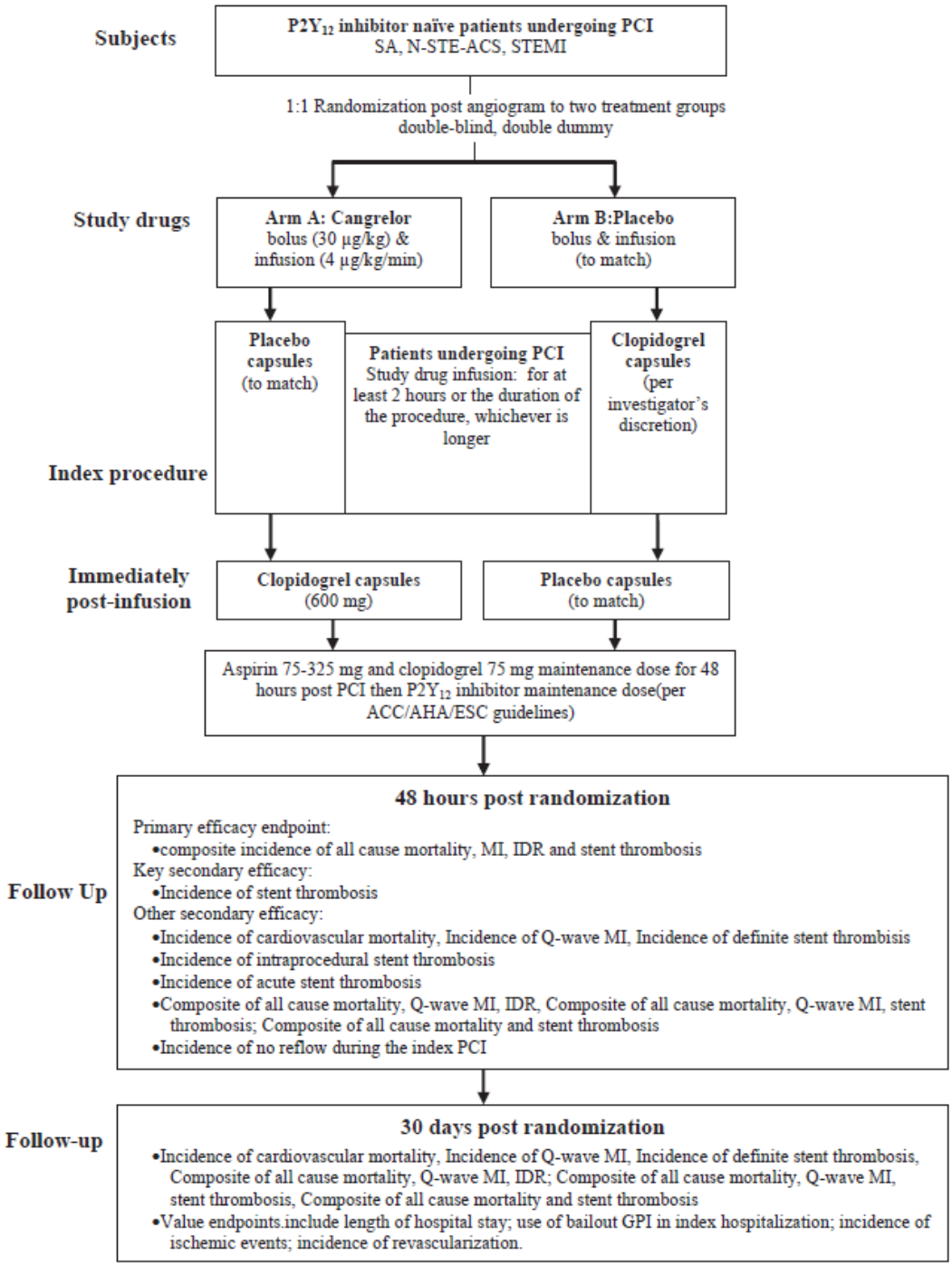
factor of ~ 6.5 fold.[10] Using a less severe bleed to assess benefit risk, such as a GUSTO moderate or TIMI minor bleed still favors the use of cangrelor.

We recommend that cangrelor be approved as an adjunct to PCI for the reduction in risk of periprocedural ischemic complications including myocardial infarction and stent thrombosis in patients in whom treatment with an oral $P2Y_{12}$ platelet inhibitor prior to PCI is not feasible and when glycoprotein IIb/IIIa receptor antagonists are not anticipated to be used.

10 GUSTO severe bleed is an intracranial hemorrhage or bleeding resulting in hemodynamic compromise.

7 Appendices

7.1 CHAMPION PHOENIX Trial design and follow-up



Source: CHAMPION PHOENIX CSR

7.2 Definitions

Table 14. Bleeding definitions in CHAMPION PHOENIX

Bleed Classification	Definition
GUSTO severe	• Intracranial bleeding or • Resulting in hemodynamic compromise requiring treatment (includes fatal bleeding)
GUSTO moderate	• Requiring blood transfusion
GUSTO mild	• Other bleeding requiring intervention, but not requiring transfusion or causing hemodynamic compromise
TIMI major†	• Intracranial bleeding or • Any bleeding associated with clinically overt signs associated with a drop in hemoglobin of > 5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit > 15%)
TIMI minor†	• Clinically overt sign of bleeding (including observations by imaging techniques) that is associated with a fall in hemoglobin of ≥3 g/dL and ≤5 g/dL (or when hemoglobin is not available, an absolute drop in hematocrit ≥9% and ≤15%)
ACUITY major†	• Intracranial bleeding or • Intraocular bleeding or • Retroperitoneal or • Access site hemorrhage requiring intervention or • ≥ 5 cm diameter hematoma or • Reduction in Hg ≥ 4 g/dL without an overt source of bleeding or • Reduction in Hg ≥ 3 g/dL with an overt source of bleeding or • Reoperation for bleeding or • Use of any blood product transfusion
ACUITY minor	• All other bleeding not listed as major

Myocardial Infarction Definition in CHAMPION PHOENIX (UDMI, 2007)
Type 1 = Spontaneous MI related to ischemia due to primary coronary event
Type 3 = Sudden unexpected cardiac death, often with symptoms suggestive of myocardial ischemia accompanied by new ECG changes or with ischemic evidence by angiography or autopsy.
Type 4a = MI associated with PCI
Type 4b = MI associated with ST.
There was no Type 2 or Type 5 MIs.

Society for Cardiovascular Angiography and Interventions (SCAI) MI Definition
SCAI MI in patients with normal baseline cardiac biomarkers is a post PCI MI with CK MB ≥10x ULN or CK MB ≥5x ULN (or cardiac troponin ≥35x ULN) with new pathologic Q-waves in ≥ 2 contiguous leads (or new persistent left bundle branch block) or cardiac Troponin I or T ≥70x ULN.

To diagnose post-PCI MI in ACS patients in whom the baseline level has not returned to normal:
1) In patients with elevated cTn (or CK-MB) in whom the biomarker levels are stable or falling, there should be a new CK-MB elevation by an absolute increment of ≥10x ULN (or ≥70x ULN for cTn I or T) from the previous nadir level;
2) In patients with elevated cTn (or CK-MB) in whom the biomarker levels have not been shown to be stable or falling, there should be a further rise in CK-MB or troponin beyond the most recently measured value by an absolute increment of ≥10x ULN in CK-MB or ≥70x ULN in cTn plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

7.3 Literature Review/References

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Levine, G, et al., 2011, 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, JACC, 58 (24): e44-e122

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Thygesen, K, et al., 2007, Universal Definition of Myocardial Infarction, Circulation, 116:2634-2653

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/s/

BACH N BEASLEY
03/19/2015

FORTUNATO F SENATORE
03/19/2015

STEPHEN M GRANT
03/19/2015

U.S. Department of Health and Human Services

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences

Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 204-958 (SN 0063)
Drug Name:	Cangrelor
Indication(s):	Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)
Applicant:	The Medicines Company
Date(s):	Date of Document: December 23, 2014 PDUFA due date: June 23, 2015
Review Priority:	6 month resubmission
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Efficacy Reviewer: Fortunato Senatore, MD, PhD Safety Reviewer: Nhi Beasley, PharmD
Project Manager:	Alison Blaus

Keywords: landmark analysis, site-reported events

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1. INTRODUCTION

1.1 Overview

Reference is made to the Agency's Complete Response for the Cangrelor New Drug Application NDA 204958 on April 30, 2014. After subsequent meetings, the sponsor resubmitted the NDA with additional analyses and information to address the issues raised in the Complete Response letter.

The statistical review for this re-submission mainly focuses on several items in CHAMPION PHOENIX trial

1. Landmark analysis
2. Sensitivity analyses on the primary composite endpoint (removing intraprocedural stent thrombosis from the primary composite endpoint, using more conservative definition of MI, et al)
3. Efficacy analyses on site-reported primary endpoint
4. Discrepancies between Sponsor's results and Dr. Marciniak's results

1.2 Data Sources

The analysis datasets of CHAMPION PHOENIX resubmission is located at \\CDSESUB1\evsprod\NDA204958\0063\m5\datasets\tmc-can-10-01-crlresp\analysis\legacy\datasets.

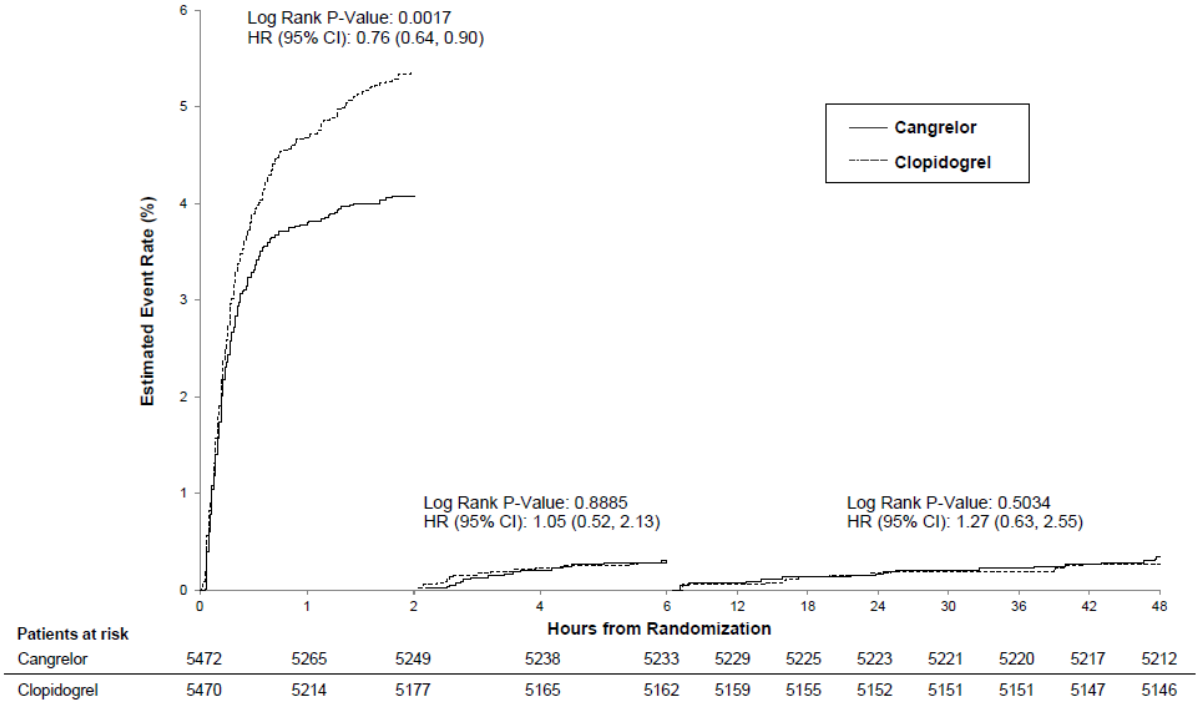
2. STATISTICAL EVALUATION

2.1 Landmark Analysis

The sponsor provided landmark analysis to demonstrate that essentially all of the difference in primary events rates between the randomized groups was in the first 2 hours after randomization. The primary endpoint events were divided into those which occurred within 2 hours after randomization, those which occurred between 2 hours and 6 hours, and those between 6 hours and 48 hours. Figure 1 is the landmark analysis based on the protocol-defined primary endpoint (Death/MI/IDR/ST). To further examine the robustness of the results, the sponsor performed

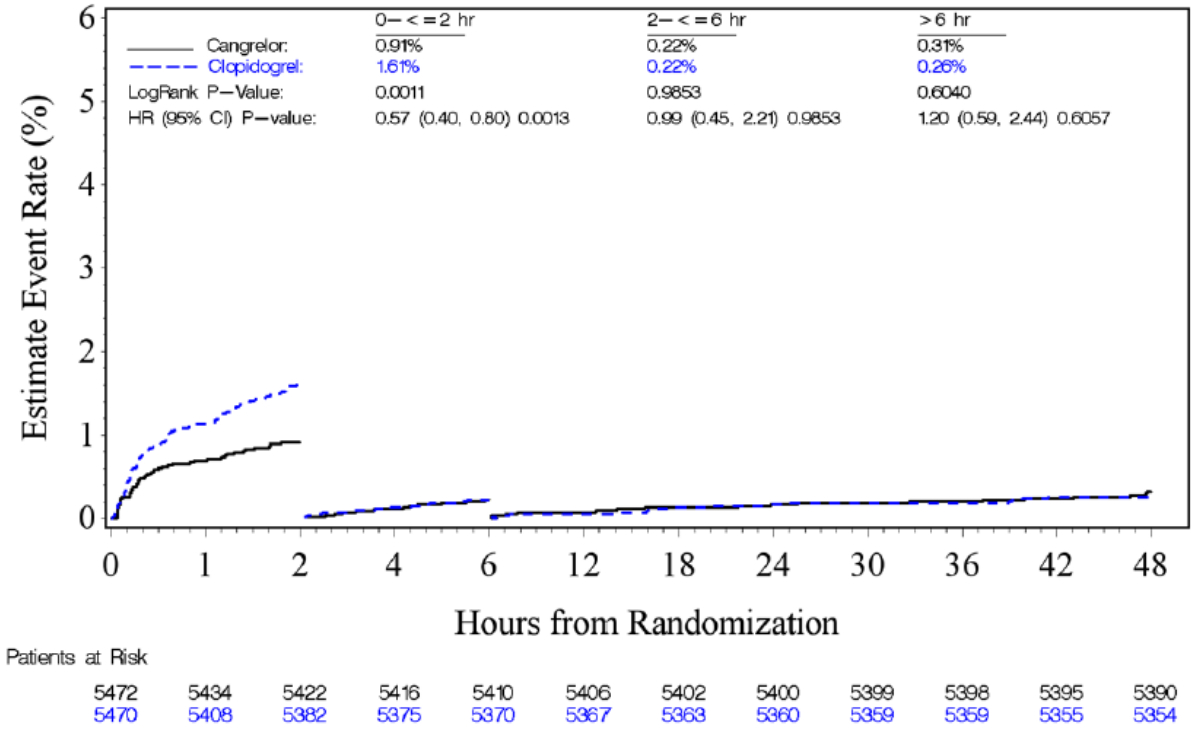
similar landmark analysis using a supplemental primary endpoint that excluded IPST and used a more conservative definition of MI (Death/SCAI MI/IDR/ARC-ST), which was shown in Figure 2. Table 1 listed the total number of events in each treatment group for every time period in the landmark analyses. The reviewer was able to verify all the results.

Figure 1: Landmark analysis on First Occurrence of Death/MI/IDR/ST



[Source: Figure 6 in Sponsor's response document, confirmed by the reviewer]

Figure 2: Landmark Analysis on First Occurrence of Death/SCAI MI/IDR/ARC-ST



[Source: Figure 105.1.1.1.312 in Sponsor's response dated Feb 17, 2015, confirmed by the reviewer]

Table 1: Total Patients and Patients with Events in Landmark Analyses

Endpoint	Period	Treatment Group	Patients with 1st Events	Total Number of Patients
Death, MI, IDR, and ST	0-2 hr	Cangrelor	223	5472
		Clopidogrel	293	5470
	2-6 hr	Cangrelor	16	5249
		Clopidogrel	15	5177
	6-48 hr	Cangrelor	18	5233
		Clopidogrel	14	5162
Death, SCAI MI, IDR, and ARC ST	0-2 hr	Cangrelor	50	5472
		Clopidogrel	88	5470
	2-6 hr	Cangrelor	12	5422
		Clopidogrel	12	5382
	6-48 hr	Cangrelor	17	5410
		Clopidogrel	14	5370

[Source: Table 3 in Sponsor's response dated Feb 23, 2015, confirmed by the reviewer]

It was also noted that among the 138 Death/SCAI MI/IDR/ARC-ST events that occurred within 2 hours, 65 subjects (43 in clopidogrel arm and 22 in cangrelor arm) had a composite event of

Death/SCAI MI/IDR/ARC-ST within 5 minutes from infusion of the study drug (Table **11**). Of these 65 adjudicated events, 24 of them (17 in clopidogrel arm and 7 in cangrelor arm) were also reported at site. The site-reported time of these 24 events was later than the event time determined by CEC (many of them were a few hours or even a few days later). The sponsor stated that CEC determined the event time at the earliest time point according to the specific information for each event type.

The reviewer further examined the 138 Death/SCAI MI/IDR/ARC-ST events included in the first two-hour landmark analysis. Out of the 138 adjudicated events, 76 events (51 events in clopidogrel arm and 25 events in cangrelor arm) were also reported by site. If calculated by the event time recorded at site, 32 events of these 76 events (22 in clopidogrel and 10 in cangrelor) occurred beyond 2 hours after randomization.

The sponsor's landmark analysis was based on the event time determined by CEC. This may explain why the sponsor's landmark analysis only found treatment effect in the first 2 hours but not after 2 hours.

2.2 Sensitivity analyses on the adjudicated primary composite endpoint

To address the issue that some subcomponents of the primary endpoint may not represent clinical benefit, the sponsor performed additional sensitivity analyses. Table 2 and Table 3 showed results by excluding IPST and using several more conservative definitions of MI. The point estimate of all the sensivity analyses were trending to the right direction and showed consistency compared to the protocol-defined primary endpoint. Cangrelor does not appear to affect death rate.

Table 2: Protocol-Defined and Supplemental Primary Endpoints at 48 Hours (mITT)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Death	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52, 1.92)	0.9996
MI	207/5470 (3.8)	255/5469 (4.7)	0.80 (0.67, 0.97)	0.0224
IDR	28/5470 (0.5)	38/5469 (0.7)	0.74 (0.45, 1.20)	0.2167
ST[1]	46/5470 (0.8)	74/5469 (1.4)	0.62 (0.43, 0.90)	0.0101
Supplemental Primary Endpoints				
Death/MI (SCAI definition)/IDR/ARC-ST	79/5470 (1.4)	114/5469 (2.1)	0.69 (0.52, 0.92)	0.0110
MI by SCAI definition	53/5470 (1.0)	81/5469 (1.5)	0.65 (0.46, 0.92)	0.0149
ARC-ST	12/5470 (0.2)	22/5469 (0.4)	0.54 (0.27, 1.10)	0.0858
Death/MI (CK-MB ≥ 10X ULN)/IDR/ARC-ST	77/5470 (1.4)	111/5469 (2.0)	0.69 (0.51, 0.92)	0.0123
MI (CK-MB ≥ 10X ULN)	50/5470 (0.9)	78/5469 (1.4)	0.64 (0.45, 0.91)	0.0128

[1]Includes ARC-ST and IPST. Adjusted for loading dose and baseline patient status in logistic regression.

[Source: Table 12 in Sponsor's response document, confirmed by the reviewer]

Table 3: Sensitivity Analyses of the Primary Endpoint at 48 Hours (mITT)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Removal of IPST				
Death/MI/IDR/ARC-ST	230/5470 (4.2)	286/5469 (5.2)	0.80 (0.67, 0.95)	0.0115
Removal of IPST and MIs Identified Solely by CK-MB Elevations >3X ULN but < 10X ULN[2]				
Death/MI/IDR/ARC-ST	106/5470 (1.9)	161/5469 (2.9)	0.65 (0.51, 0.83)	0.0007
Removal of IPST and all MIs Identified Solely by CK-MB Elevations[3]				
Death/MI/IDR/ARC-ST	86/5470 (1.6)	130/5469 (2.4)	0.66 (0.50, 0.86)	0.0025
Removal of IPST and all MIs				
Death/IDR/ARC-ST	43/5470 (0.8)	54/5469 (1.0)	0.79 (0.53, 1.19)	0.2615

1Includes ARC-ST and IPST. Adjusted for loading dose and baseline patient status in logistic regression.
2Includes peri-procedural MIs with one of the following: CK-MB ≥10X ULN or MI with either ischemic symptoms or 12-lead ECG changes).
3Includes peri-procedural MIs identified by either ischemic symptoms or 12-lead ECG changes.

[Source: Table 14 in the Sponsor's response document, confirmed by the reviewer]

Table 2 listed the counts of the individual components of the protocol-defined primary endpoint based on all events occurred within 48 hours. To avoid double counting, the reviewer calculated the counts of individual components by assigning each subject only one type of event. For those subjects who had more than one type of event at the same time, the more severe event would be used. For example, if a patient had a MI and ST at the same time, only MI would be counted. The reviewer follow the order of death > MI > IDR > ST. Table 4 showed the individual component counts for a number of composite endpoints.

Table 4: Individual Component Counts for the Composite Endpoints

	protocol-defined primary endpoint				
	Composite	Death	MI	IDR	ST
clopidogrel	322	14	254	11	43
cangrelor	257	12	204	9	32
	Death/SCAI MI/IDR/ARC-ST				
	Composite	Death	SCAI MI	IDR	ARC ST
clopidogrel	114	16	81	13	4
cangrelor	79	15	50	12	2
	removal of IPST and MIs (identified Solely by CKMB>3ULN but <10ULN) from the primary endpoint				
	Composite	Death	MI	IDR	ST
clopidogrel	161	16	130	11	4
cangrelor	106	15	80	9	2

[Source: reviewer's analysis]

The sensitivity analyses of the primary endpoint showed in Table 2 and Table 3 were all based on mITT population. The reviewer also performed similar analyses in the ITT population (Table 5). The conclusion, nevertheless, remains unchanged.

Table 5: Supplemental Primary Endpoint at 48 Hours (ITT population)

Endpoint	cangrelor (N=5581)	clopidogrel (N=5564)	OR and 95% CI
protocol-defined primary endpoint	260	325	0.79 (0.67, 0.93)
Death/SCAI MI/IDR/ARC-ST	82	117	0.70 (0.52, 0.92)
SCAI MI	53	81	0.65 (0.50, 0.92)
ARC-ST	12	22	0.54 (0.27, 1.10)
Death/MI (CKMB>=10ULN)/IDR/ARC-ST	80	114	0.70 (0.52, 0.93)
MI (CKMB>=10ULN)	50	78	0.64 (0.45, 0.91)
removal of IPST	233	289	0.80 (0.67, 0.95)
removal of IPST and MIs (CK-MB elevations >3ULN but < 10ULN)	109	164	0.66 (0.51, 0.84)
removal of IPST and all MIs (CKMB elevations)	89	133	0.66 (0.51, 0.87)
removal of IPST and all Mis	46	57	0.80 (0.54, 1.19)

[Source: reviewer's analysis]

2.3 Site-reported Events

The reviewer verified sponsor's site reported results. The sponsor submitted the SAS program used to derive site reported event from raw data and the reviewer was able to verify sponsor's results.

Table 6: Site-Reported Primary Events at 48 Hours (mITT population)

	Cangrelor (N=5472)	Clopidogrel (N=5470)	OR and 95% CI	p-value
Protocol-Defined Primary Endpoint				
Death/MI/IDR/ST[1]	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66, 0.93)	0.0049
Site-Reported Events				
Death/MI/IDR/ST[2]	96/5470 (1.8)	121/5469 (2.2)	0.79 (0.60, 1.03)	0.0862
Death/MI/IDR/ST (IDR eCRF)[3]	94/5470 (1.7)	118/5469 (2.2)	0.79 (0.60, 1.04)	0.0957

1. Includes ARC-ST and IPST.
2. Includes MIs recorded by the site on the MI eCRF page, IDR recorded by the site on the Revascularization eCRF page, and ST from death, MI, IDR, Follow-up, and PCI eCRF pages.
3. Includes MIs recorded by the site on the MI eCRF page, unplanned revascularizations recorded by the site on the Revascularization eCRF page, and ST recorded by the site on the IDR eCRF.

[Source: Table 15, confirmed by the reviewer]

2.4 Discrepancies between Sponsor's results and Dr. Marciniak's results

In the Advisory Committee Meeting on February 12, 2014, Dr. Marciniak presented his analysis results based on site-reported events, which showed discrepancies with what the sponsor presented. The reviewer extracted the dataset used by Dr. Marciniak from his reviews and further examined Dr. Marciniak's analyses and sponsor's analyses. Table 7 is sponsor's results based on mITT population, which were presented by the sponsor during the AC meeting. Table 8 is based on ITT population and Table 9 is Dr. Marciniak's results, which is also based on ITT population. The patient types listed in the three tables were based on the investigator's initial assessment of clinical presentation as entered into the IVRS, not the derived patient type.

Table 7: Sponsor's Results on Primary endpoint by Index Events (mITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	clopidogrel	cangrelor
Angina	217/3172 (6.8%)	182/3186 (5.7%)	65/3172 (2.1%)	52/3186 (1.6%)
UA/NSTEMI	82/1428 (5.7%)	53/1464 (3.6%)	37/1428 (2.6%)	26/1464 (1.8%)
STEMI	23/870 (2.6%)	22/822 (2.7%)	16/870 (1.8%)	16/822 (2.0%)
All	322/5470 (5.9%)	257/5472 (4.7%)	118/5470 (2.2%)	94/5472 (1.7%)

Table 8: Sponsor's Primary endpoint by Index Events (ITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	Clopidogrel	cangrelor
angina	217/3208 (6.8%)	182/3220 (5.7%)	65/3208 (2.0%)	53/3220 (1.7%)
UA/NSTEMI	82/1435 (5.7%)	53/1479 (3.6%)	37/1435 (2.6%)	27/1479 (1.8%)
STEMI	26/921 (2.8%)	25/882 (2.8%)	20/921 (2.2%)	21/882 (2.4%)
All	325/5564 (5.8%)	260/5581 (4.7%)	122/5564 (2.2%)	101/5581 (1.8%)

Table 9: Tom's Results on Primary endpoint by Index Events (ITT population)

	adjudicated primary endpoint		site-reported primary endpoint	
	Clopidogrel	Cangrelor	clopidogrel	Cangrelor
angina	217/3208 (6.8%)	182/3220 (5.7%)	68/3208 (2.1%)	58/3220 (1.8%)
UA/NSTEMI	82/1435 (5.7%)	53/1479 (3.6%)	37/1435 (2.6%)	32/1479 (2.2%)
STEMI	26/921 (2.8%)	25/882 (2.8%)	21/921 (2.3%)	25/882 (2.8%)
all	325/5564 (5.8%)	260/5581(4.7%)	126/5564 (2.3%)	115/5581 (2.1%)

The ITT population in PHOENIX trial comprised 5581 patients in the cangrelor arm and 5564 patients in the clopidogrel arm. Among those in the ITT population, 109 patients in the cangrelor arm and 94 patients in the clopidogrel arm did not receive study drug or did not undergo the index PCI procedure and were excluded from the mITT population. The mITT population thus consisted of 5472 patients in the cangrelor arm and 5470 patients in the clopidogrel arm. The major difference on site-reported events between mITT population and ITT population is in STEMI patients. Using mITT population, the site-reported event rates in STEMI patients were 1.8% in clopidogrel arm and 2.0% in cangrelor arm. Using ITT population, the site-reported event rates in STEMI patients were 2.2% in clopidogrel arm and 2.4% in cangrelor arm. In both cases, the cangrelor arm had a slightly higher event rate than clopidogrel arm. However, the results based on subgroups need to be interpreted with caution.

Dr. Marciniak included 18 extra events in his analyses on the site-reported events. As a result, site-reported event rates in his analyses were 2.8% in cangrelor arm and 2.3% in clopidogrel arm. These 18 subjects were listed in Table 10. Of these 18 subjects who were not reported by the investigators at site but were considered having a primary event at 48 hours by Dr. Marciniak, only one subject was adjudicated to have a primary endpoint event at 48 hours. Further details and discussions about these 18 patients can be found in the clinical review by Dr. Senatore and Dr. Beasley.

Table 10: Extra Subjects with Events at 48 Hours by Dr. Marciniak

Subject ID	Index Event	Abnormal	Site	US	Adjudicated Event 48 Hours	Adjudicated Event 30 Days	Treatment
401021013	NSTE-ACS	Yes	401021	Yes	No	No	cangrelor
401030289	Angina	No	401030	Yes	No	No	cangrelor
439001076	NSTE-ACS	Yes	439001	No	No	No	cangrelor
439001085	NSTEMI	Yes	439001	No	No	No	cangrelor
439004181	NSTE-ACS	Yes	439004	No	No	No	cangrelor
443002052	NSTEMI	Yes	443002	No	No	No	cangrelor
443002145	NSTE-ACS	Yes	443002	No	No	No	cangrelor
449001009	NSTEMI	Yes	449001	No	No	No	clopidogrel
449004029	Angina	No	449004	No	No	No	clopidogrel
449005002	NSTEMI	Yes	449005	No	No	No	cangrelor
449005032	Angina	No	449005	No	No	No	cangrelor
449012005	Angina	No	449012	No	No	No	cangrelor
449017033	Angina	No	449017	No	No	No	clopidogrel
449021003	Angina	No	449021	No	Yes	Yes	cangrelor
495002197	NSTE-ACS	Yes	495002	No	No	No	cangrelor
495005197	NSTEMI	Yes	495005	No	No	No	cangrelor
495005476	Angina	No	495005	No	No	No	cangrelor
495005567	Angina	No	495005	No	No	No	clopidogrel

Appendix

Table 11: Comparison of Adjudicated Event Time and Site Reported Event Time

Subject ID	Treatment	Randomization Time	Drug Start Time	Adjudicated Event Time	Site-reported Event Time
401001168	clopidogrel				
401010028	clopidogrel				
401010103	clopidogrel				
401011070	clopidogrel				
401025016	clopidogrel				
401027083	clopidogrel				
401028004	clopidogrel				
401030075	clopidogrel				
401030173	clopidogrel				
401030232	clopidogrel				
401055020	clopidogrel				
401058008	clopidogrel				
401058029	clopidogrel				
401077048	clopidogrel				
401079035	clopidogrel				
401079151	clopidogrel				
401079204	clopidogrel				
401085036	clopidogrel				
401091101	clopidogrel				
401091338	clopidogrel				
401091597	clopidogrel				
401092073	clopidogrel				
407012029	clopidogrel				
420003076	clopidogrel				
420009333	clopidogrel				
420009375	clopidogrel				
420009402	clopidogrel				

(b) (6)

420009485	clopidogrel	(b) (6)
420009670	clopidogrel	
420009832	clopidogrel	
420009864	clopidogrel	
439002038	clopidogrel	
449004028	clopidogrel	
449013047	clopidogrel	
449017003	clopidogrel	
459003016	clopidogrel	
459003045	clopidogrel	
459007016	clopidogrel	
495002252	clopidogrel	
495005346	clopidogrel	
495005404	clopidogrel	
495005553	clopidogrel	
495005587	clopidogrel	
401007046	cangrelor	
401029049	cangrelor	
401053011	cangrelor	
401079060	cangrelor	
401079193	cangrelor	
401091423	cangrelor	
420009059	cangrelor	
420009098	cangrelor	
420009162	cangrelor	
420009655	cangrelor	
420009695	cangrelor	
420009798	cangrelor	
420009836	cangrelor	
443002177	cangrelor	
449004044	cangrelor	
449005048	cangrelor	

		(b) (6)
449021003	cangrelor	
466001043	cangrelor	
466002056	cangrelor	
495005503	cangrelor	
495005540	cangrelor	
495005618	cangrelor	

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/s/

JIALU ZHANG
03/25/2015

PEILING YANG
03/25/2015
Signed on behalf of Dr. HM James Hung.

CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	204958
Submission Type:	Resubmission – Class 2
Submission Date:	December 23, 2014
PDUFA goal date:	June 23, 2015
Drug Name:	Cangrelor
Trade Name:	KENGREXAL®
Drug Class:	$P2Y_{12}$ antagonist
Proposed Indication:	Reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)
Applicant:	The Medicines Company
OCP Division:	DCP1
OND Division:	Division of Cardiovascular and Renal Products (DCRP)
Reviewer:	Sreedharan Sabarinath, PhD
Team Leaders:	Jeffry Florian, PhD Rajanikanth Madabushi, PhD

Table of Contents

INTRODUCTION

Cangrelor is an intravenous, reversible $P2Y_{12}$ platelet receptor antagonist that blocks adenosine diphosphate (ADP) induced plate activation and aggregation. The original new drug application (NDA) for cangrelor was submitted on 04/30/2013 and received a Complete Response letter on 04/30/2014. The applicant resubmitted the NDA on 12/23/2014 addressing the issues raised in the Complete Response letter. In addition, the current submission includes clinical pharmacology studies addressing or confirming transition strategies proposed for switching patients from cangrelor to two other oral $P2Y_{12}$ drugs: clopidogrel and prasugrel.

This review is an addendum to the clinical pharmacology review (DARRTS dated 1/10/2014), from the first review cycle, which includes detailed information on the clinical pharmacology of cangrelor. The focus of this review is primarily on labeling recommendations for transitioning patients from cangrelor to oral antiplatelet agents. The review also addresses the utility of cangrelor in patients on glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors.

RECOMMENDATIONS:

The recommended strategies for transitioning from cangrelor infusion to oral antiplatelet therapy and for Gp IIb/IIa inhibitors (GPIs) are as follows:

- Ticagrelor: administer a 180 mg loading dose during or immediately after discontinuation of cangrelor infusion. This transition represents the best choice in terms of the impact on the antiplatelet activity.
- Clopidogrel: Administer 600 mg loading dose immediately after discontinuation of cangrelor infusion. While there is a loss of antiplatelet activity for a short duration following the switch, there is clinical trial experience with this transition strategy form Phase 3.
- Prasugrel: Administer 60 mg loading dose immediately after discontinuation of cangrelor infusion.
- Glycoprotein IIb/IIIa inhibitors: Avoid concurrent use of GPIs with cangrelor. Concurrent use can increase bleeding risk. GPIs may be used as bailout rescue medication after discontinuing cangrelor infusion.

Antiplatelet Effects of clopidogrel, prasugrel and ticagrelor

Clopidogrel and prasugrel are irreversible oral $P2Y_{12}$ drugs while ticagrelor is a reversible $P2Y_{12}$ receptor blocker. The reported average pharmacological effects of these drugs, based on percentage inhibition of platelet aggregation measured using light transmittance aggregometry with 20 µM ADP as agonist, are illustrated in Figure 1 below.

Prasugrel and ticagrelor attain maximum platelet inhibition relatively faster compared to clopidogrel after a single dose administration. Similarly the maximum platelet inhibition seen with ticagrelor and prasugrel were higher relative to that observed with clopidogrel.

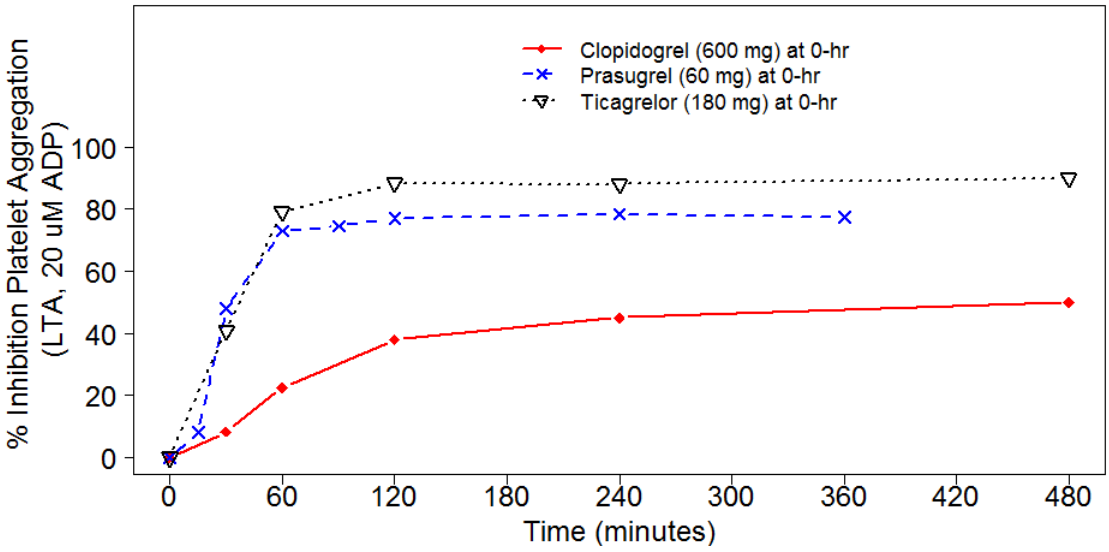

Figure 1 Percentage inhibition in platelet aggregation for clopidogrel, prasugrel and ticagrelor loading doses. Source: Adapted from approved USPI of Brilinta®[1] [ticagrelor and clopidogrel profile] and Effient®[2] [prasugrel profile].

Transition to Ticagrelor

The transition from cangrelor to ticagrelor was evaluated in study MDCO-CAN-12-13 in patients with stable coronary artery disease (reviewed previously[3]). Cangrelor was administered as 30 µg/kg IV bolus and 4 µg/kg/min 2 h infusion (note: all cangrelor administrations in the figures and descriptions below use the same bolus and infusion doses, but for brevity are referred as a

[1] Ticagrelor USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022433s010lbl.pdf

[2] Prasugrel USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022307s010lbl.pdf

[3] Clinical Pharmacology Review, DARRTS date 01/10/2014

'cangrelor infusion'). A 180 mg loading dose of ticagrelor was given at 30 minutes (90 minutes prior to the end of infusion) or 75 minutes (45 minutes prior to the end of infusion) (N=6). The inhibitory effects of cangrelor and ticagrelor were preserved when both products were co-administered (Figure 2). After discontinuing cangrelor infusion, there was a slight decrease in platelet inhibition for about 30 minutes, which is considered as not significant. Therefore, our recommendation is to administer loading dose of ticagrelor (180 mg) during or immediately after the cangrelor infusion (Figure 3).

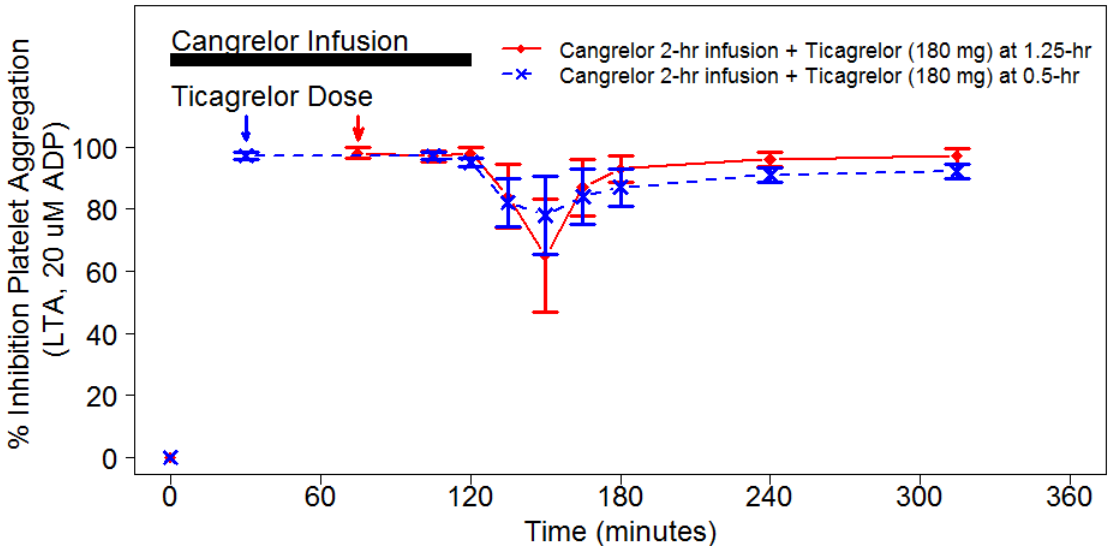

Figure 2 Transition from cangrelor to ticagrelor. The horizontal black bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of ticagrelor 180 mg dose. Error bars represent 90 % confidence intervals. Source: Prepared by FDA

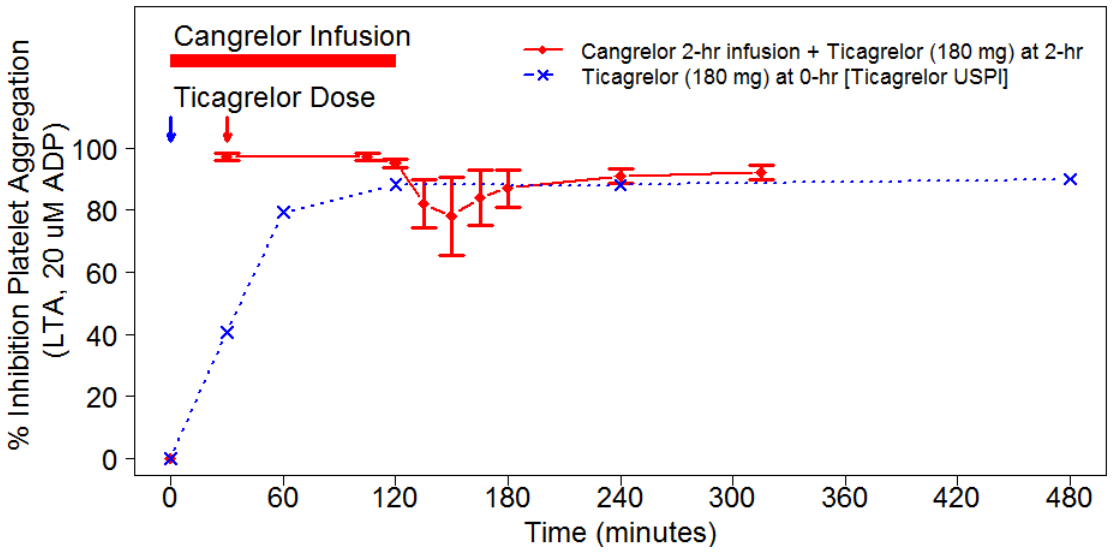

Figure 3 Recommended transition strategy for ticagrelor: administer 180 mg ticagrelor during or at the end of cangrelor infusion. The blue dotted line is a representative time-course of antiplatelet effect seen with 180 mg ticagrelor when given alone, extracted from ticagrelor USPI. The horizontal red bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of ticagrelor 180 mg dose. Error bars represent 90 % confidence intervals. There was no ticagrelor reference treatment group in ticagrelor transition studies. There was a temporary dip in antiplatelet activity for about 30 minutes after cangrelor infusion was stopped, but there was no attenuation in ticagrelor's pharmacological effects. Source: Prepared by FDA

Transition to Clopidogrel

Study TMC-CAN-04-02 (reviewed earlier[4]) was a study in healthy subjects to assess the pharmacokinetics of cangrelor and the pharmacodynamics of either clopidogrel 600 mg alone or clopidogrel 600 mg administered either at the beginning or at the end of cangrelor infusion. Platelet inhibition was measured using whole blood impedance aggregation (WBIA), p-selectin expression measured by flow-cytometry and light transmittance aggregometry (LTA). There was a significant loss in antiplatelet effects of clopidogrel when administered at the beginning of cangrelor infusion possibly because of competitive inhibition at platelet $P2Y_{12}$ receptors. The active metabolite of clopidogrel is short lived and administration of clopidogrel 1-hr prior to the end of the infusion results in maximum exposure of the active metabolite during the period

[4] Clinical Pharmacology Review, Page 29, DARRTS date 01/10/2014

when platelet inhibition with cangrelor is maintained. This minimizes the ability of the active metabolite of clopidogrel to irreversibly bind to platelets, resulting in loss of its pharmacological activity. The recommendation, based on this study, was to administer clopidogrel loading dose at the end of cangrelor infusion. It should also be noted that this transition strategy was employed for clopidogrel in the CHAMPION-PHOENIX pivotal efficacy study.

In study MDCO-CAN-13-02 in patients with stable coronary artery disease (CAD), additional scenarios evaluating clopidogrel loading dose administered during the 2 h cangrelor infusion period were evaluated. The dosing times were at 2 h (end-of-infusion) (N=3), at 1.5 h (0.5 h prior to the end of the infusion) (N=6) and at 1 h (1-h prior to the end of the infusion) (N=3). The study results are shown in Figure 4.

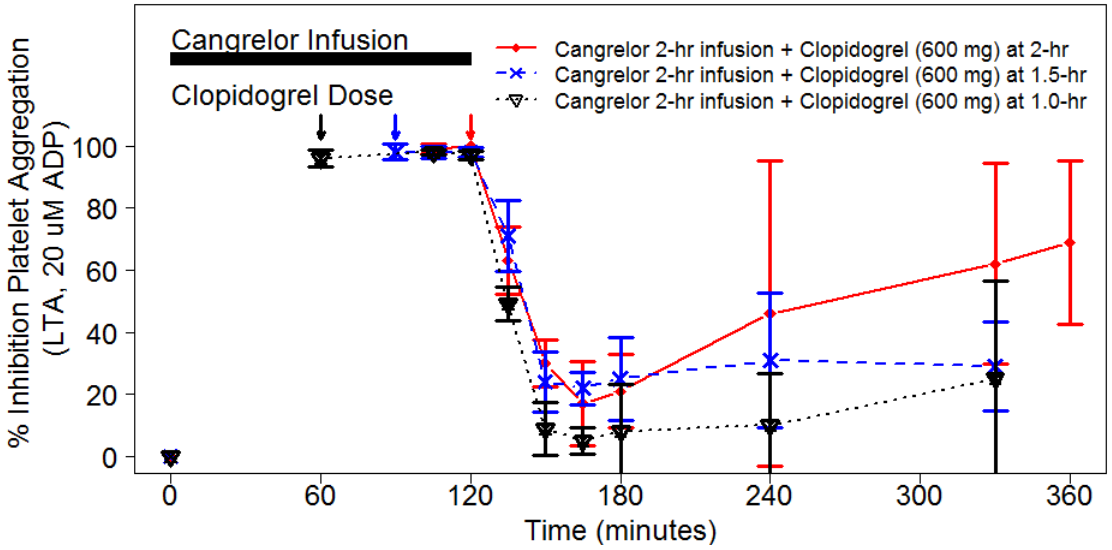

Figure 4 Percentage inhibition in platelet aggregation time-course with cangrelor and clopidogrel measured by LTA. Error bars represent 90 % confidence intervals. The horizontal black bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of clopidogrel 600 mg dose. Baseline measurements at zero time reflect no drug treatment. Administering clopidogrel 600 mg loading dose after stopping cangrelor infusion did not alter its expected pharmacological effect. However, administering clopidogrel during cangrelor infusion resulted in significant attenuation of its antiplatelet effect. Source: Prepared by FDA

When the dosing time for clopidogrel overlapped with cangrelor infusion there was profound attenuation in clopidogrel's antiplatelet effect. These results in CAD patients are in agreement with the previously reviewed transition study TMC-CAN-04-02 in healthy subjects. Therefore,

the recommended transition strategy for clopidogrel is to administer a 600 mg loading dose immediately after stopping cangrelor infusion (Figure 5) as detailed in our previous review[5].

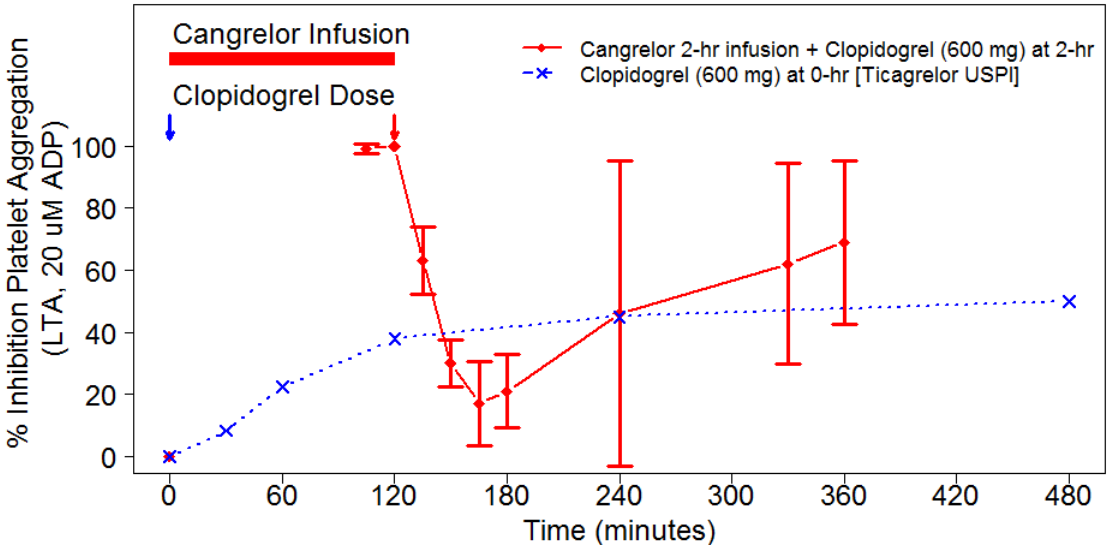

Figure 5 Recommended transition strategy for clopidogrel: administer 600 mg clopidogrel loading dose at the end of cangrelor infusion. The horizontal red bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of clopidogrel 600 mg dose. Error bars represent 90 % confidence intervals. The blue dotted line is a representative time-course of antiplatelet effect seen with 600 mg clopidogrel when given alone, extracted from ticagrelor USPI. There was no clopidogrel reference treatment group in study MDCO-CAN-13-02. There was a temporary dip in antiplatelet activity after cangrelor infusion was stopped, but there was no attenuation in clopidogrel's pharmacological effects. Source: Prepared by FDA

[5] Clinical Pharmacology Review, Page 29, DARRTS date 01/10/2014

Transition to Prasugrel

Prasugrel (60 mg) was administered at 1 h (1-h prior to the end of infusion) (N=3) or 1.5 h (0.5-h prior to the end of infusion) (N=6), or 2 h (at the end of the cangrelor infusion) (N=3) in study MDCO-CAN-13-01 in patients with CAD. Study MDCO-CAN-13-02 also tested transition from cangrelor to prasugrel where a prasugrel 60 mg loading dose was given 30 min after end of cangrelor infusion (N=3). The observed time course of platelet response is shown in Figure 6.

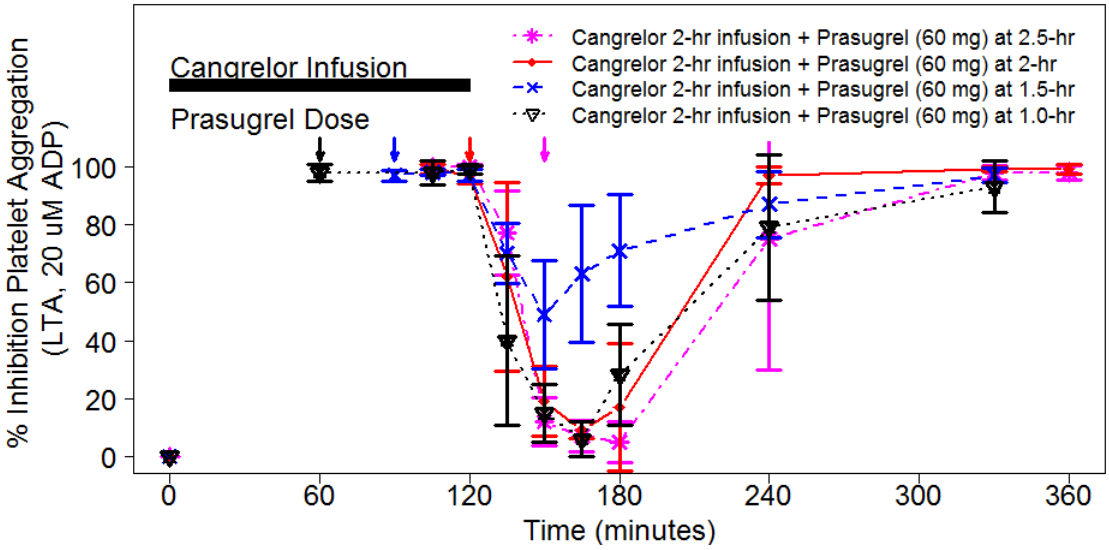

Figure 6 Percentage inhibition of platelet aggregation with prasugrel and cangrelor. The horizontal black bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of prasugrel 60 mg dose. Error bars represent 90 % confidence intervals. This figure includes data from studies MDCO-CAN-13-01 and MDCO-CAN-13-02. Source: Prepared by FDA

Administration of prasugrel at 1.5 h (0.5 h prior to the end of the cangrelor infusion) limited the recovery of platelet activity to a greater extent after stopping cangrelor infusion. Prasugrel dosed at 1 h (1 h prior to the end of infusion) or at 2 h (end of infusion) allowed complete recovery of platelet activity to baseline (drug free) levels at 2-4 h. As seen in MDCO-CAN-13-01 there was also complete recovery of platelet activity to baseline levels when prasugrel was given at 2.5 h (0.5 h after stopping cangrelor infusion). All prasugrel treatment groups showed antiplatelet effects similar to that seen with cangrelor from 4 h time point onwards. Prasugrel showed higher than reported pharmacological response, on par with cangrelor, in this study (Figure 6). However, this is likely due to comparison of results between different studies.

Further, the prasugrel switch study results appear to suggest that administration at 1.5 h (0.5 h prior to the end of the cangrelor infusion) would minimize the period of time when platelet inhibition is less than maximal and that administration at either the end of infusion or 1 h prior to the end of the infusion would result in the similar platelet inhibition profiles. However, the clinical pharmacology review team has difficulty reconciling the observations for prasugrel in MDCO-CAN-13-01 and MDCO-CAN-13-02 with what was observed for clopidogrel in MDCO-CAN-13-02 and TMC-CAN-04-02 and what is known about the clinical pharmacology for prasugrel and clopidogrel.

The active metabolite of prasugrel is reported to have half-life greater than 2 h. As such the metabolite would be expected to be in systemic circulation even if the prasugrel dose was administered 1 h prior to the end of the infusion resulting in a less substantial decrease in platelet inhibition than observed. On the contrary, if the active metabolite was no longer systemically available with administration 1 h prior to the end of the infusion, it is not possible to explain similar platelet inhibition profile to that observed with administration of prasugrel at 2 h (end of the infusion).

Moreover, it's difficult to explain why administering prasugrel 0.5 h prior to the end of the cangrelor infusion would results in greater platelet inhibition given the expected onset time of the active metabolite and as the inhibition in this scenario appear magnified compared to administration at the end of the infusion (as opposed to time-shifted), we consider the observations in this arm a result of small sample size (n=3 or 6) and that making dosing recommendations based on this study is not justified. Since prasugrel belongs to the same class as that of clopidogrel, a reasonable approach would be to use prasugrel the same way as clopidogrel, when transitioning. Therefore, our recommendation is to administer loading dose of prasugrel immediately after stopping cangrelor infusion (Figure 7). An additional study which is appropriately powered would be needed to inform any other transition approaches with prasugrel.

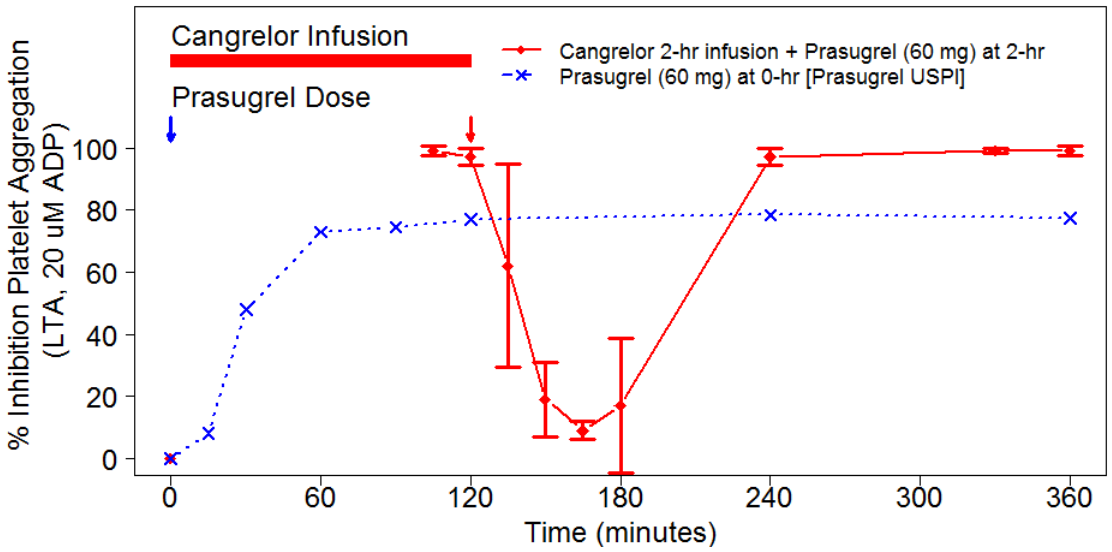

Figure 7 Recommended transition strategy for prasugrel: administer 60 mg prasugrel at the end of cangrelor infusion. The blue dotted line is a representative time-course of antiplatelet effect seen with 600 mg clopidogrel when given alone, extracted from prasugrel USPI. The horizontal red bar indicates 2 h-infusion duration for cangrelor. The down arrows color matched to the plot lines indicate administration of prasugrel 60 mg dose. Error bars represent 90 % confidence intervals. There was no prasugrel reference treatment group in prasugrel transition studies. There was a temporary dip in antiplatelet activity after cangrelor infusion was stopped, but there was no attenuation in prasugrel's pharmacological effects. Source: Prepared by FDA

A plot of time course of antiplatelet effect seen with the recommended transition strategies for all the three drugs are shown in Figure 8.

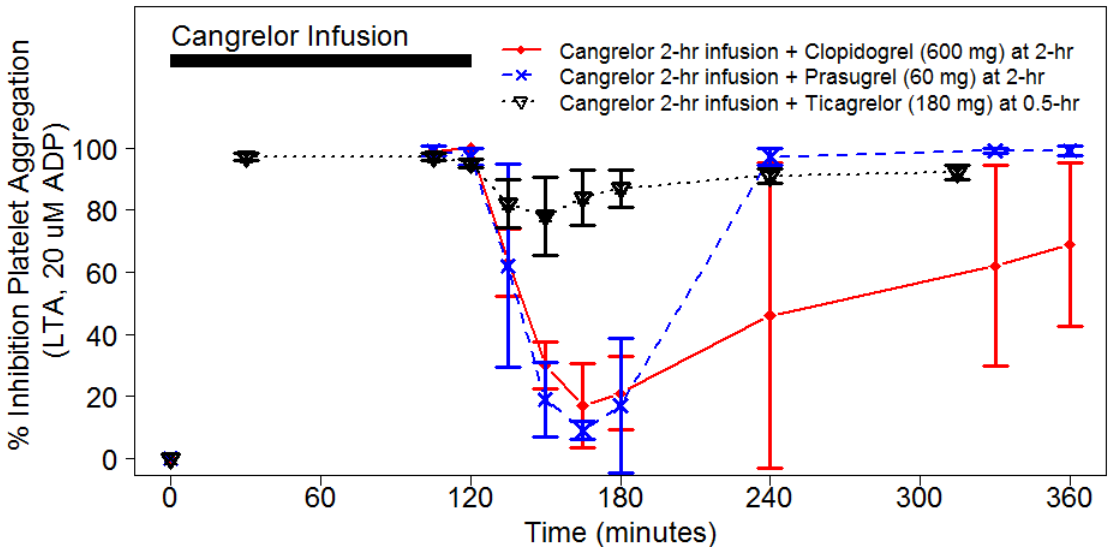

Figure 8 Recommended transition strategies for clopidogrel, prasugrel and ticagrelor. The horizontal black bar indicates 2 h-infusion duration for cangrelor. Error bars represent 90 % confidence intervals. Source: Prepared by FDA

Cangrelor with glycoprotein IIb/IIIa inhibitors

Mechanistic Expectation:

Cangrelor is a reversible platelet inhibitor that blocks binding of ADP to platelet $P2Y_{12}$ receptors, one of the pathways for activation of platelet-Gp IIb/IIIa complex. In a broad sense, drugs that inhibit Gp IIb/IIIa receptors act downstream in the platelet activation/aggregation cascade relative to platelet $P2Y_{12}$ receptor blockers[6]. Therefore, if platelet activation by ADP is blocked (by drugs like clopidogrel, prasugrel, ticagrelor or cangrelor) conformational changes to Gp IIb/IIIa receptors that induce binding to fibrinogen may not occur. Based on this hypothesis, the clinical consequence of administering cangrelor to patients on Gp IIb/IIIa inhibitors (GPIs) is expected to be minimal. However, there are no pharmacokinetic/pharmacodynamic or drug-drug interaction studies in the sponsor's original or current submissions that support this hypothesis.

[6] Circulation, 1995, 92:2373-2380. http://circ.ahajournals.org/content/92/9/2373.full

Clinical Experience:

There is limited clinical data on GPI use from the three CHAMPION Phase III studies. GPIs were allowed only as bail out therapy in the pivotal efficacy study CHAMPION-PHOENIX. The two other Phase III studies that failed to demonstrate clinical benefits for cangrelor, CHAMPION-PLATFORM and CHAMPION-PCI, both initially allowed GPI use at investigator's discretion but later actively discouraged their use by means of protocol amendments. Reported actual GPI use was 2.3 %, 8 % and 22 % in PHOENIX, PLATFORM and PCI studies, respectively[7]. The use of GPIs did not appear to affect treatment effect of cangrelor relative to clopidogrel for primary efficacy endpoint in all these studies, but the observed event rates were relatively higher in patients with GPI use than those without[8].

Observed bleeding events in the first 48 hours from CHAMPION-PCI study for patients with and without GPI use are listed below in Table 1. Patients with GPI use had higher incidence of GUSTO severe/life threatening and TIMI major bleeds for both cangrelor and clopidogrel treatment groups. The PCI study had about 22 % of patients on GPIs. CHAMPION-PLATFORM study also showed a similar trend but had fewer patients on GPIs (8 %). The clinical experience for cangrelor use with GPIs, predominantly from CHAMPION-PCI study, suggests an increase in bleeding risk with concurrent use. This is consistent with the USPIs of GPIs (tirofiban[9], abciximab[10], and eptifibatide[11]) which suggest an increased bleeding risk for GPIs when co-administered with antiplatelet drugs.

Table 1 **Comparison of bleeding events between patients with and without GPI use from CHAMPION-PCI study**

GUSTO Severe/Life Threatening Bleeds n/N (%)		
	Cangrelor	Clopidogrel
GPI use	4/1154 (0.3)	6/1170 (0.5)
No GPI use	6/3219 (0.2)	5/3194 (0.2)
TIMI Major Bleeds		
GPI use	15/1154 (1.3)	10/1170 (0.9)
No GPI use	4/3219 (0.1)	4/3149 (0.1)

Source: Adapted from Clinical Study Report TMC-CAN-05-02, CHAMPION-PCI, Pages 100-102

[7] Division Director Review, Page 3, DARRTS dated 4/30/2014

[8] Statistical Review, Page 8, DARRTS dated 4/23/2014

[9] AGGRASTAT® (tirofiban): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020912s019s020lbl.pdf

[10] ReoPro® (abciximab): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103575s5126lbl.pdf

[11] INTEGRILIN® (eptifibatide): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020718s037lbl.pdf

While the USPIs of ticagrelor[12] and prasugrel[13] allow concomitant use with GPIs, the usage setting is almost similar to the way cangrelor is proposed to be used. Cangrelor and GPIs are intravenous short acting drugs with a quick onset. Hence, there does not seem to be a situation that requires administration of both cangrelor and GPIs at the same time.

Therefore, our recommendation is not to use GPIs concurrently with cangrelor during PCI. However, GPIs can be used for bail out rescue medication, as done in the pivotal efficacy study CHAMPION-PHOENIX.

[12] BRILINTA® (ticagrelor): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022433s010lbl.pdf

[13] EFFIENT® (prasugrel): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022307s010lbl.pdf

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